Aspects of child health and their links to psychological outcome measures : results from a national cohort of young twins

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Academic dissertation submitted to the University of London

for the degree of Doctor of Philosophy (Ph. D.)

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March 2003

Acknowledgements

The work described in this dissertation would have taken far longer to complete without the encouragement and support from many people. It is a delight to acknowledge those who have supported me over the last years.

First of all, I would like to thank my supervisor Robert Plomin for his ongoing support, for providing me with so many great opportunities and for giving me the inspiration to write this. His guidance, suggestions and encouragement helped enormously in bringing this thesis to completion.

A large share of successful research is due to a pleasant and fruitful working and learning environment. I am particularly thankful for the help and advice of Thalia Eley and Louise Webster when I first started working at the Centre. Thank you to my colleagues and all my fellow students at the SGDP for the conversations and for sharing thoughts, as well as pizzas and pints, especially to Essi Viding, Sheila Walker, Alessandra Iervolino and Mike Galsworthy for their companionship and advice. Special thanks also go to Tara McKearney for her tremendous support throughout the whole writing up process and for being there for me whenever I needed a helping hand.

I would also like to thank the whole TEDS team for working some very long days and nights to collect and process the data. Sharing countless cups of tea made the office feel like a second home. Special thanks go also of course to the twins and their families for their continuing participation in TEDS. Without them and the joint efforts of Bonny Oliver and Alexandra Trouton, the past and present project co-coordinators of TEDS, this dissertation would not have been possible.

Work and life is only enjoyable with friends and family. Several have accompanied me along the way and the days would have passed far more slowly without their support and encouragement. Thank you to my brother Matthias, my sisters Julia and Kathrin and to my very good friends Micky Faber and Alan Hodgson. Special thanks go to my dear friend Maya von Witzleben for keeping my spirits up during the difficult stages and for being so incredibly helpful with everything *not* concerning this dissertation.

I am particularly grateful to Dieter Weinbrenner without whose continuous help and support things would have been so much harder. Finally I would like to thank my mother for continually helping me in every possible way. My father Michael will always share a part of my soul, and I dedicate this work to him.

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List of Publications

Published or in press

Koeppen-Schomerus, G., Spinath, F. M., & Plomin, R. (2003). Twins and non-twin siblings: Different estimates of shared environmental influence in early childhood. Twin Research, 6 .

Koeppen-Schomerus, G., Stevenson, J., & Plomin, R. (2001). Genes and environment in asthma: a study of 4 year old twins. Archives of Disease in Childhood, 85, 398-400.

Koeppen-Schomerus, G., Wardle, J., & Plomin, R. (2001). A genetic analysis of weight and overweight in 4-year-old twin pairs. International Journal of Obesity & Related Metabolic Disorders, 25, 838-844.

Koeppen-Schomerus, G., Eley, T. C., Wolke, D., Gringras, P., & Plomin, R. (2000). The interaction of prematurity with genetic and environmental influences on cognitive development in twins. Journal of Pediatrics, 137, 527-533.

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Koeppen-Schomerus, G., Stevenson, J. & Plomin, R. (2001). A twin study of genetic and environmental factors in asthma and its impact on behaviour in four-year-olds. Society of Behavioral Medicine, 22nd Annual Meeting, Seattle, Washington, USA.

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Koeppen-Schomerus, G., Eley, T. C., Wolke, D. F., Gringras, P., & Plomin, R. (1999). The interaction of gestational age and environmental influences on cognitive and language development in 2-year-old twins. 20th Annual Conference, Society for Reproductive and Infant Psychology, Hatfield, Hertfordshire, UK.

Koeppen-Schomerus, G., Stevenson, J. & Plomin, R. (2001). A Twin Study of Genetic and Environmental Factors in Asthma and its Relationship with Behaviour Problems in four-year-olds. 15th Annual Conference, European Health Psychology Society & Division of Health Psychology (BPS), St. Andrews, Scotland, UK.

Koeppen-Schomerus, G., Stevenson, J., & Plomin, R. (2001). A twin study of genetic and environmental factors in the relationship between asthma and behaviour in four-year-olds. 10th International Congress on Twin Studies, London, UK.

List of Abbreviations

All abbreviations are also defined at the time of first use in the text.

a^2	Variance of a trait explained by additive genetics
ACE model	Genetic model estimating additive genetic (A), shared/common environmental (C) and non-shared environmental (E) effects
ADE model	Genetic model estimating additive genetic (A), non-additive/dominance genetic (D) and non-shared environmental (E) effects
AD	Atopic dermatitis (eczema)
AIC	Akaike's Information Criterion
ANOVA	Analysis of variance
BMI	Body Mass Index (kg/m^2)
c^2	Variance of a trait due to shared/common environmental effects
CI	Confidence Interval
d^2	Variance of a trait due to non-additive/dominance genetic effects
DNA	Deoxyribonucleic acid
DF	DeFries-Fulker
df	Degrees of freedom
DZ	Dizygotic
DZf	Dizygotic same-sex female
DZm	Dizygotic same-sex male
DZos	Dizygotic opposite-sex (i.e. male-female)
DZss	Dizygotic same-sex
e^2	Variance of a trait due to non-shared/unique environmental effects
EEA	Equal environments assumption
GxE	Genotype-Environment interaction
h^2	Heritability estimate
MCDI	McArthur Communicative Development Inventory
MZ	Monozygotic
MZf	Monozygotic female
MZm	Monozygotic male
OM	Otitis media
PARCA	Parent Report of Cognitive Abilities
RRPSPC	Revised Rutter Parent Scale for Preschool Children
QTL	Quantitative Trait Locus
SD	Standard deviation
TEDS	Twins Early Development Study

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Abstract

The focus of this dissertation is to investigate the genetic and environmental aetiology of the onset and early stages of four medical disorders in childhood – i.e. asthma, eczema, otitis media (OM) and overweight - and their relationship with measures of behavioural development in a large population sample of twins using parent-reports and assessments at 2, 3 and 4 years of age.

For all four health phenotypes under investigation, heritability increased with age whereas shared environment had little or no influence. Analyses of body weight showed substantial heritability to both individual differences in weight throughout the distribution (48-54%) and to the mean weight difference between overweight children and the rest of the population (35-60%). Shared environmental factors were moderate (23-44%). Asthma was also substantially influenced by genetic factors (78-79%) whereas shared environmental influences were small and not statistically significant. For eczema, univariate genetic analyses indicate high heritability (76-87%) in the absence of shared environmental effects. Otitis media (OM) showed substantial heritability which increased from age 1.5 (48%) to age 4 years (71%) with moderate influence of shared environment which declined with age.

Virtually no differences existed between affected and unaffected children for developmental measures of cognition and language. For behaviour problems, there were weak associations with asthma and eczema which are likely to be mediated by nonshared environment. OM showed moderate yet significant correlations with behaviour problems at ages 2 (r=.19), 3 (r=.26) and 4 years (.30). Bivariate genetic analyses indicated that the association between OM and behaviour problems is mediated largely by shared environment rather than by genetic overlap.

The current findings are a first step towards a better understanding of the aetiology of childhood diseases and their relationship with behavioural development. In the future, it is important to continue to combine genetic, medical and psychological concepts as such interdisciplinary studies are likely to provide new insights into the complex interplay between nature and nurture as they relate to health and behavioural development.

1 Introduction

1.1 Overview

This chapter introduces the disciplines of behavioural genetics and health psychology, with a brief overview from their beginnings up until today. This is followed by a discussion of how the relationship between both fields has developed and its implications for current and future research. Finally, a brief focus is provided on how this dissertation contributes to some of the issues introduced.

1.2 Behavioural Genetics

The 20th century saw the birth of genetics as a mature science. Through the rediscovery of Mendel's Laws at the beginning of the last century and the research that followed, DNA was confirmed as the substance of heredity by the mid 1940s. This was followed by the report of Watson and Crick on the structure of DNA as a double helix (Watson & Crick, 1953) with the capability to replicate itself. Finally, the end of the last century was celebrated with the transcription of a complete draft of the DNA sequence of the human genome (Venter et al., 2001; International Human Genome Sequencing Consortium, 2001).

Behavioural genetics is the study of genetic and environmental influences on an organism's behaviour and has been defined as:

> *"A theory of multiple gene influences that, together with environmental variation, result in quantitative (continuous) distributions of phenotypes. Quantitative genetic methods such as the twin and adoption design for human analysis and inbred strain and selection studies for non-human analysis, estimate genetic and environmental contributions to phenotypic variance within a population."* (Plomin, DeFries, McClearn, & McGuffin, 2001, p.61)

It includes both molecular genetic techniques used for identifying and mapping specific genes or markers, and quantitative genetic methods such as

family, twin and adoption studies to disentangle the relationship between genetics (*nature*) and environment (*nurture*). The results of quantitative genetic research can guide molecular genetic researchers targeting those traits that are most promising for finding genetically informative markers (Plomin & Crabbe, 2000).

During the past few decades there has been a shift in the behavioural sciences from seeing "genetics" and "environment" as two mutually exclusive entities. Up until the middle of the last century psychologists believed that human behavioural traits were almost exclusively the result of environmental influences. It was thought that, although genetic factors were of importance in infancy and childhood, the effects of environmental experiences eventually dominated the shaping of personality traits and behavioural characteristics. In fact, behavioural genetic findings suggest the opposite: for many traits genetic effects increase rather than decrease with age (Plomin et al., 2001; McCartney, Harris, & Bernieri, 1990). Similarly, environmental effects that are shared between family members tend to decrease as children get older. In fact, for many psychological traits unique environmental experiences that contribute to differences rather than similarities between siblings or parents and offspring are found to become increasingly important with age (Plomin & Daniels, 1987; Plomin, Asbury, & Dunn, 2001).

The inception of behavioural genetics as a new field for research has contributed to the discipline of psychology as a whole better recognising and appreciating the importance of genetic factors on psychological traits. Today, behavioural genetics has become a plank of psychology as it places the field at the intersection of the biological and behavioural sciences.

1.3 Health Psychology

The application of psychology to the prevention of disease, the management and the promotion of our health has emerged as one of the most exciting and challenging tasks of the 21st century. The fact that this discipline has

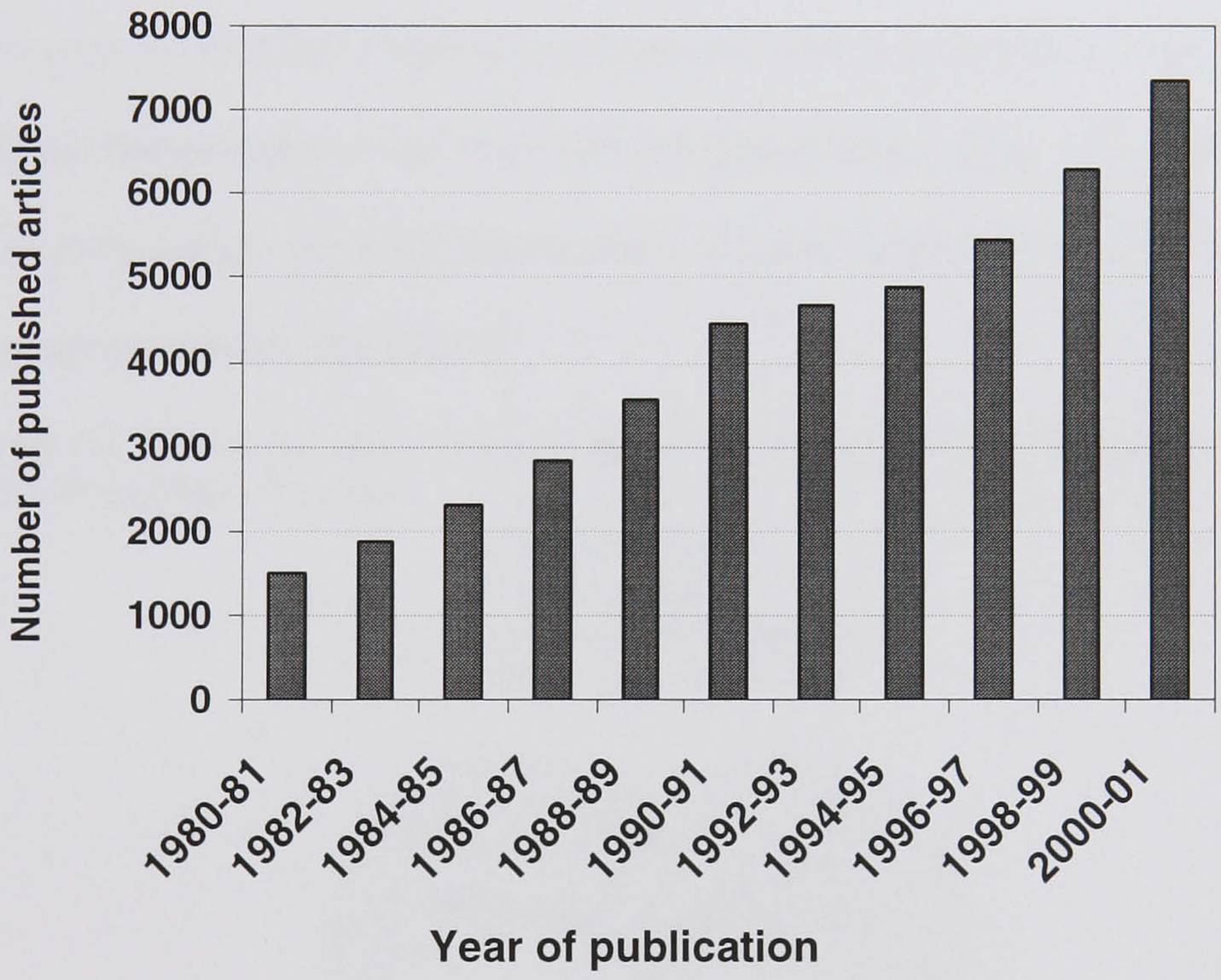
only been awarded Division status within the British Psychological Society (BPS) in 1997 reflects the increasing need and value of applying insights in psychology to health and health care practice. Over the last decades, health psychology has contributed to identifying individual behaviours and lifestyles that affect a person's physical health, the prevention and treatment of illness, the identification of factors associated with ill-health, and the improvement of health care systems and shaping public opinion with regard to people's health (Bennett, Weinman, & Spurgeon, 1990; Baum, Revenson, & Singer, 2001).

From a historical point of view, an important shift in thinking about disease occurred at the beginning of the last century. Instead of physical illness being viewed as the equivalent to a person having 'a diseased body', illness was also considered as interacting with and affecting a person's behaviour and psychological well-being. In other words, disease was no longer perceived as the outcome of organic malfunctioning or biochemical changes, but as the result of additional influences including psychological factors. Through this change in perception, disciplines such as psychosomatic medicine, behavioural medicine, behavioural health and health psychology were born during the 1970s. Since then, these disciplines have increased the awareness of the role of psychological factors in relation to health and disease.

Thus health psychology has asserted itself as a specialised field within general psychology which focuses on the interplay between mind and body in relation to physiological health. Research in health psychology explores how people's emotions, thoughts, behaviours, and social interactions influence physical well being. In contrast to the closely related disciplines, psychosomatic medicine, behavioural medicine and behavioural health, health psychology particularly emphasises the application and exploration of psychological processes in relation to health and disease.

There has been a steady growth in the number of articles published in health psychology and related disciplines. A literature search based on the Medical Literature Analysis and Retrieval System Online (MEDLINE®) and the Psychological Abstracts (PsycINFO) databases from 1980-2001 revealed that the number of publications in health psychology and related areas has increased more than ten-fold over a period of only two decades (see Fig. 1.1)[1]. The growing popularity and importance of these health related disciplines is not only reflected by the number of specialist peer-reviewed journals, but also in the number of scientific conferences and other meetings which pursue topics related to health.

Figure 1.1: Literature search using MEDLINE® and PsycINFO databases: Increase in the number of published articles in Health Psychology and related areas over a 20 year period.



Health psychology is distinguished from most other fields of psychology by its expectation that the research and work in this field will contribute to improving health. Health psychology has been defined as

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[1] full details of the literature search are enclosed in Appendix 1

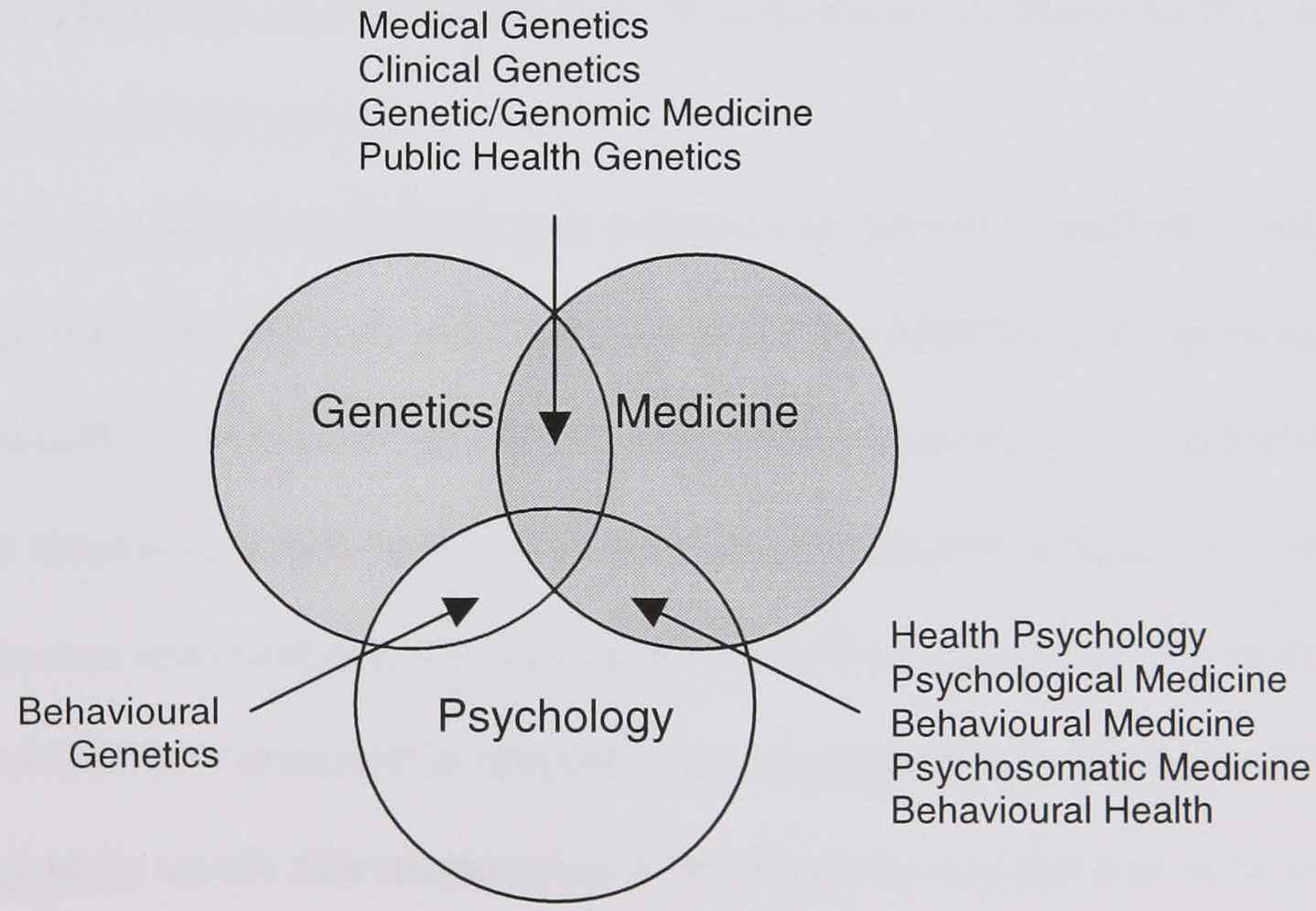
> *"…the aggregate of the specific educational, scientific, and professional contributions of the discipline of psychology to the promotion and maintenance of health, the prevention and treatment of illness, and the identification of etiologic and diagnostic correlates of health, illness, and related dysfunction."* (Matarazzo, 1980, p.4)

In summary, health psychology is devoted to understanding the psychological influences on how people stay healthy, why they become ill and how they respond when they do get ill (Taylor, 1999).

1.4 The Integration of Behavioural Genetics and Health Psychology

The study of human behaviour as it relates to health and disease is at the core of health psychology and related disciplines (i.e. psychological medicine, behavioural medicine, behavioural health and psychosomatic medicine). Behavioural genetics assesses the genetic and environmental contributions towards behavioural traits. The Venn diagram below (Fig. 1.2) shows how the three core areas -genetics, medicine and psychology- are interconnected and how they relate to both disciplines.

Figure 1.2: The interrelation between genetics, medicine and psychology and current areas of interdisciplinary overlap



In essence, *behavioural genetics* links psychology and biology. *Health psychology* and related disciplines connect psychology with the medical sciences.

The importance of interdisciplinary research between health psychology and behavioural genetics is suggested by common concepts and research aims. The link between genetics and medicine is facilitated by *medical genetics* (also known as genetic medicine, clinical genetics and genomic medicine), the study of genetic or biological variation as it pertains to health and disease in humans. Medical genetics uses molecular genetic analyses (such as DNA genotyping) to identify individuals and families at risk for certain diseases.

Currently, the role of medical genetics is to contribute to the maintenance of health by testing for Mendelian disorders and for the detection and early diagnosis of several other diseases such as cancers that have a marked genetic component.

Another related discipline which has emerged only over the last few years is *public health genetics*. Rather than applying a family and individual based approach, public health genetics aims to maintain and improve the health and well-being on a population level by proposing the implementation of large scale genetic screening programmes. At present such large screening programmes have not been put into practice, and therefore the consequences for the individual and society are as yet unknown.

How are health psychology and behavioural genetics related? Health psychology is concerned with exploring the ways in which human behaviour relates to health and disease. Behavioural genetic research provides the means to assess the degree to which health and disease related phenotypes are influenced by genetics and environment. Furthermore, behavioural genetics can help to identify *how* human behaviour is related to certain health and disease phenotypes, i.e. the degree to which this relationship is mediated by nature and nurture.

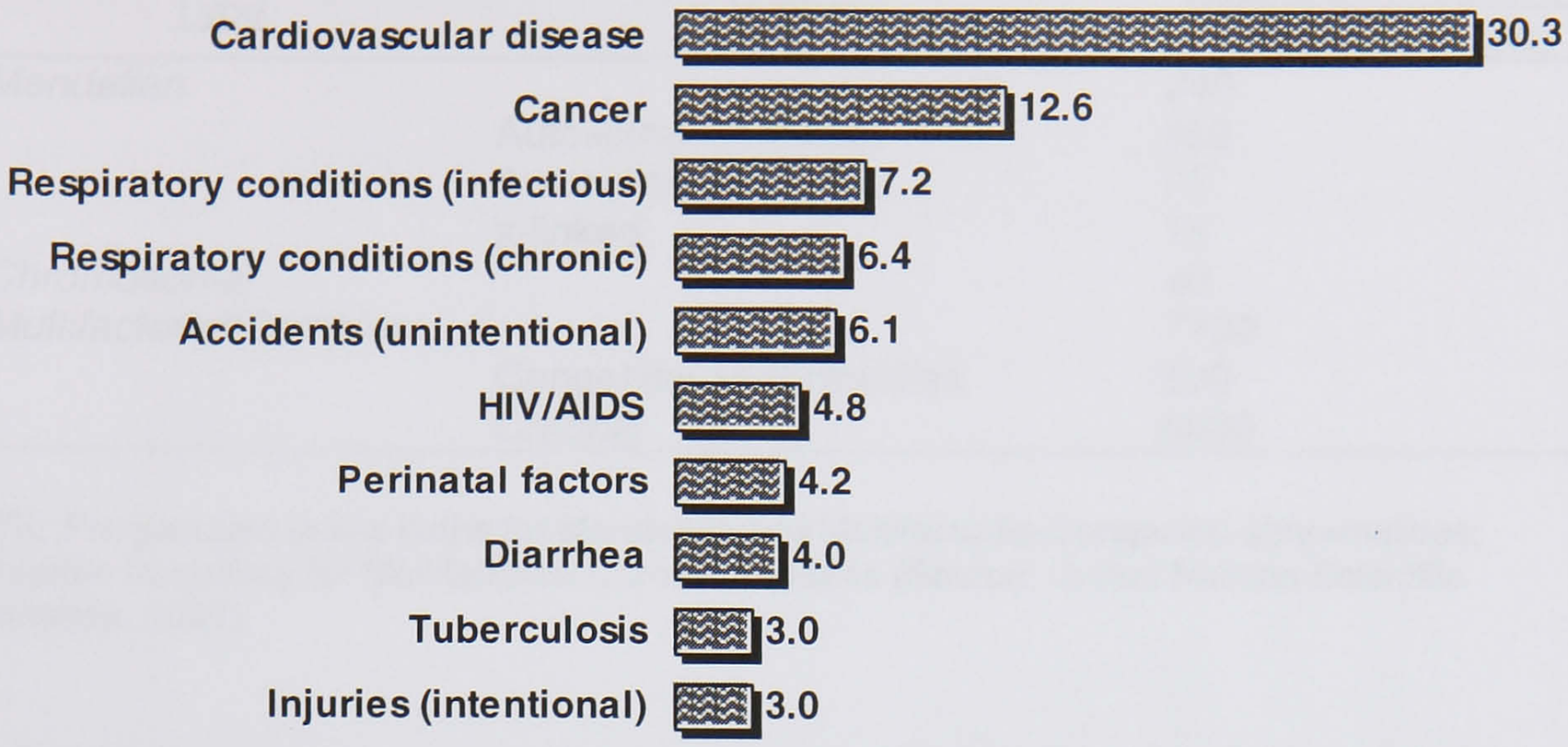
In order to better understand the aetiology of diseases and in particular how they relate to behaviour and psychological traits, it is important to combine

genetic, medical and psychological theories, as it is here that new insights will most likely be discovered.

Despite its shared theoretical links with the natural sciences such as medicine and biology, health psychology has only just started to acknowledge the role and importance of genetics. In the past, genetic disorders were thought to be caused by either an extra or missing chromosome or by a mutation in a single gene. As genetic disorders were thought to be relatively rare, they were considered to be important to only a minority of affected individuals or families. Because of their relatively small impact on national health these conditions were of limited interest.

Over the last century, patterns of disease have changed substantially due to vast improvements in sanitation and hygiene as well as housing conditions. Infectious diseases such as tuberculosis, pneumonia and influenza were once the leading causes of death and resulted in high rates of infant mortality and a low life expectancy (Eiser, 1997; World Health Organization, 2003). Changes in living conditions, the development and discovery of antibiotics and other medical advances have turned many previously fatal infectious diseases into treatable conditions, and some illnesses (e.g. polio, smallpox, diphtheria) have virtually disappeared in western countries. As the rate of infectious disease has declined and life expectancy has risen, there has been a corresponding increase in the number of people suffering from chronic illness at some time during their life. Today, chronic or non-communicable diseases have become the most prominent of healthcare concerns and are the leading factors in causing disability and mortality in the population (World Health Organization, 2003). The bar chart below (Fig. 1.3) illustrates this trend and shows that cancer and cardiovascular disease taken together account for more than 40% of worldwide mortality today.

Figure 1.3: Percentages of leading causes of death worldwide (World Health Organization, 2003)



For many chronic conditions, the origins are largely unknown. The majority of studies report on adult samples where the condition under investigation has already been established and so understanding the development of the disease/disorder is more troublesome. A better understanding of the early stages of these chronic conditions in childhood would correct this knowledge gap. In addition to chronic diseases, the health of today's children is undermined by a number of essentially preventable problems (e.g. poor diet, inadequate prenatal conditions relating to maternal health, passive smoking etc).

The involvement of genetic factors has been reported for many diseases. Although there are rare single-gene disorders, the majority of human diseases are complex and a result of an interaction between genetic variations and environmental factors (e.g., diet, infectious agents, toxic chemicals etc). A recent report by the United Nations Scientific Committee (United Nations Scientific Committee, 2001) suggests that today more than 7000 diseases have a multifactorial or complex genetic basis (see Table 1.1). In complex heritable diseases multiple genetic loci and multiple environmental factors determine disease risk and disease expression.

Table 1.1: Types and Baseline Frequencies of Genetic Diseases in Humans

Type	Subtype	Estimated Frequency (per 10^4 persons)
Mendelian		*240*
	Autosomal dominant	150
	Autosomal recessive	75
	x-linked	15
Chromosomal		*40*
Multifactorial/Complex		*7100*
	Congenital abnormalities	600
	Chronic	6500

NOTE: Frequencies in live births for Mendelian and Multifactorial-Congenital abnormalities; population frequency for Multifactorial Chronic diseases (Source: United Nations Scientific Committee, 2001).

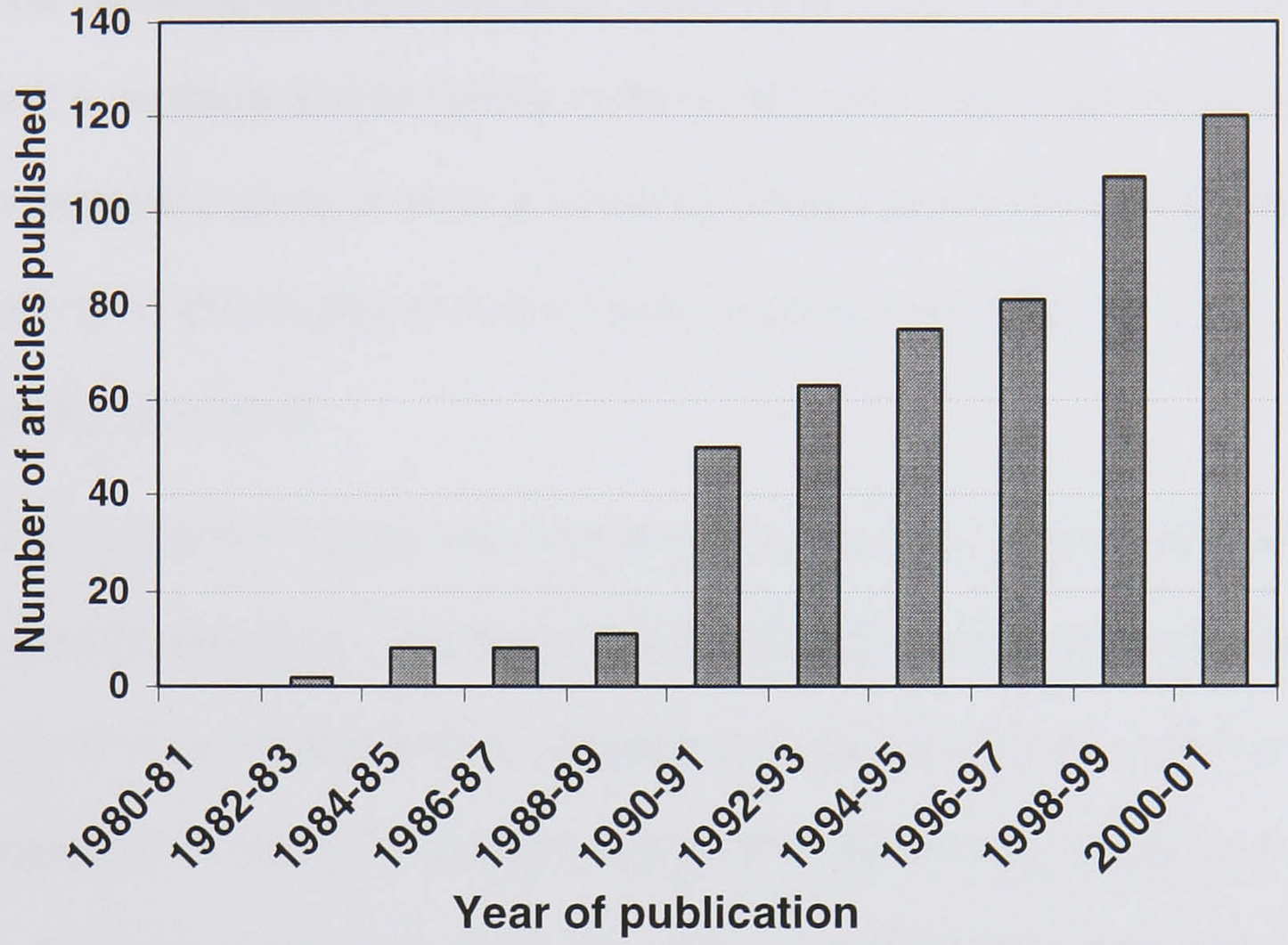
Findings from twin and family studies have firmly established the role of genetics in complex diseases such as diabetes (Redondo, Fain, & Eisenbart, 2001; Field, 2002), heart disease (Scheuner, 2001; Luft, 2001), and respiratory disease (Los, Postmus, & Boomsma, 2001; Walter, Gottlieb, & O'Connor, 2000; Joos, Pare, & Sandford, 2002). Cancer shows much less genetic influence (Lichtenstein et al., 2000; Hemminki & Li, 2002).

Despite their apparent commonalities it is surprising that there is still relatively little overlap between research in behavioural genetics and health psychology. Health psychologists have in the past paid very little attention to the importance of genetics in health and disease. Health psychology is a relative newcomer to genetic research. Only during the last few years has the importance of genetic influences on behaviours as well as certain illnesses been recognised by health psychologists which is reflected in the slowly increasing number of interdisciplinary articles between health psychology and behavioural genetics (see Fig. 1.4)[2]. The blending of both health psychology's applications and theories with behavioural genetics knowledge of the role of genes and the environment, is a

[2] see Appendix 1 for full details

powerful tool in explaining the aetiology of major health problems but also crucially in devising effective intervention strategies.

Figure 1.4: Literature search using MEDLINE® and PsycINFO databases: Number of interdisciplinary articles between the areas of behavioural genetics and health psychology published during the last 20 years



2 Definitions, Epidemiology and Aetiology

2.1 Overview

The following sections consider definitions and prevalence of atopic disorders (i.e. asthma and eczema), otitis media, and overweight/obesity and provide a general outline of what is currently known about the various factors implicated in the aetiologies of these health related phenotypes.

2.2 Atopic Disorders

The concept of 'atopy' has frequently been used to denote a potential link between allergic diseases. The term 'atopy' itself (derived from the Greek *atopos,* meaning 'out of place') refers to a familial hypersensitivity of the mucous membranes and/or the skin against a range of environmental substances in the presence of increased immunoglobin E (IgE) production. The most common atopic disorders today include asthma, eczema (also sometimes called atopic dermatitis) and hay fever (also called allergic rhinoconjunctivitis or allergic rhinitis). Because hay fever was not assessed within the current study, the following sections will only focus on asthma and eczema.

2.2.1 Asthma

Asthma is a chronic inflammatory disorder of the bronchial system that is characterised by reversible airway obstruction and increased airway irritability usually accompanied by an inflammation of bronchial tissues, mucus congestion or by spasms and constriction of the airway's smooth muscles (National Heart Lung and Blood Institute, 1997). In susceptible individuals, the inflammation causes recurrent episodes of wheezing, breathlessness, and chest tightness. Asthma attacks tend to occur particularly at night or in the morning and are usually associated with airflow obstruction which is often reversible either spontaneously

or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness which is often accompanied by an allergic response to a variety of environmental stimuli or triggers. These triggers have been related to the recurrence and the severity of attacks and include factors such as physical exercise (Cummiskey, 2001; Anderson & Daviskas, 2000), exposure to air pollutants (D'Amato, 2002; Salvi, 2001), tobacco smoke (von Mutius, 2002; Lodrup Carlsen & Carlsen, 2001) as well as stressful life events (Kilpelainen, Koskenvuo, Helenius, & Terho, 2002; Lehrer, Feldman, Giardino, Song, & Schmaling, 2002).

2.2.1.1 Prevalence of asthma

Asthma affects about 150 million people worldwide and is the most prevalent chronic condition of childhood (World Health Organization, 2002). In Europe there are presently two large epidemiological studies which have facilitated a comparison between countries of the prevalence rates and the factors relating to asthma: The European Community Respiratory Health Survey (ECRHS) (ECRHS, 1996; Janson et al., 2001; ECRHS II Steering Committee, 2002) is a resource for asthma prevalence in adults and the International Study of Asthma and Allergies in Childhood (ISAAC, 1998) compares asthma rates for children. The estimated global prevalence of childhood asthma is 14.3% (Mallol, Clayton, Asher, Williams, & Beasley, 1999). For Western Europe, this rate is somewhat higher at 16.9% (Mallol et al., 1999). The UK, a country with one of the highest asthma rates worldwide, has an estimated prevalence of over 20% (ISAAC, 1998; Office for National Statistics, 2000).

Based on the findings of international epidemiological studies of asthma prevalence, the following general trends can be observed:

1) The prevalence rates for asthma (and atopic disorders) are rising worldwide

2) Asthma is more prevalent in Western countries as compared to developing countries

3) Asthma is getting more common in developing countries that are in transition to become more westernised

2.2.1.2 Risk Factors for the Development of Asthma

The risk factors implicated in the development of asthma include a variety of known risk factors ("established") as well as other factors that have found to be connected to asthma more recently ("new").

"Established" risk factors – Factors that have commonly been associated with the development of asthma include environmental allergens, air pollution, parental smoking, dietary as well as genetic factors.

Environmental Allergens – The most common allergens that are known to trigger asthma attacks in susceptible individuals include those of house dust mites, pollen and domestic animals (Busse & Lemanske, Jr., 2001; Cookson, 1999). Exposure to those allergens is thought to result in atopic sensitisation and is likely to be linked not only to the development of asthma but also to that of other atopic disorders.

Parental smoking – The direct and indirect exposure to tobacco smoke is considered a principal risk factor for the development of asthma and other respiratory diseases. Even prenatally, maternal smoking has been associated with reduced lung function in children (Lodrup Carlsen et al., 2001). Similarly, environmental exposure to tobacco smoke in the home has also been linked to increased asthma severity in children (Strachan, 2000; Cook & Strachan, 1999). Although tobacco smoke exposure is a contributing factor to asthma, it is still unclear during which periods the respiratory system is particularly vulnerable to tobacco smoke exposure and the underlying mechanisms involved are unknown.

Air Pollution – In the popular imagination, asthma is strongly associated with air pollution. While it is true that high air pollution and ozone levels can exacerbate existing asthma, air pollution levels in most westernised countries have been decreasing whereas at the same time the prevalence of asthma has been increasing. The perception of air pollution and asthma changed with the work of von Mutius and colleagues (von Mutius et al., 1994) who compared the prevalence rates of asthma in schoolchildren between East and West Germany shortly after reunification. Although in the East the levels of air pollution were significantly higher than in the West, the opposite was found for asthma prevalence: In the 'clean' West asthma rates were found to be higher than in the 'polluted' East. Subsequent follow up results suggest that although the prevalence of atopy has increased in the former East Germany, asthma rates continue to remain significantly lower as compared to the former West (Weiland et al., 1999).

Genetics – In addition to environmental factors twin and family studies have found consistent evidence that the risk of developing asthma is substantially influenced by genetic factors.

Table 2.1 summarises the main findings from twin studies of asthma to date. There are considerable differences in asthma prevalences between studies. These are likely to be due to geographical variation as well as variation in asthma definitions and assessments used by different studies. It is remarkable that, despite the differences in assessments and samples, substantial heritability on asthma is reported across studies ranging from 44 up to 79%. For a more detailed account of twin studies on asthma the reader is referred to a recent review for a more in depth discussion of such findings (Los et al., 2001).

Susceptibility to asthma is likely to be complex implying that multiple genes contribute to disease risk. Studies involving genome scans including conventional linkage and fine mapping approaches suggest that asthma is determined by

several genes of moderate effect size (CSGA, 1997; Haagerup et al., 2002; Wjst et al., 1999). Furthermore, positional cloning approaches have recently identified two genes of potential importance, namely AS1 (Hakonarson et al., 2002) and ADAM33 (Van Eerdewegh et al., 2002). So far, chromosomes 5, 6, 7, 11, 12, 14, 16 and 22 have been implicated in the aetiology of asthma (Laitinen et al., 2001; Tattersfield, Knox, Britton, & Hall, 2002).

Table 2.1 Twin studies estimating the heritability of asthma

Study's author & year of publication	Country	Method	Definition	Population Source	$N_{(pairs)}$	Age (years)	Prevalence	Heritability
Edfors-Lubs, 1971	Sweden	Q	Ever asthma	Population registry	6996	42-81	3.8%	63%
Duffy, Martin et al 1990	Australia	Q	Ever asthma or wheezing	Recruited registry	3808	18-88	13.4%	60-75%
Nieminen, Kaprio & Koskenvuo 1991	Finland	RL	Medical diagnosis	Population registry	13 888	18-70+	2.5%	44%
Lichtenstein & Svartengren 1997	Sweden	Q	diagnosed or recurrent asthma	Population registry	1480	7-9	10.0%	62-76%
Harris, Magnus et al 1997	Norway	Q	Ever asthma	Population registry	2932	18-25	5.7%	75%
Laitinen, Rasanen et al 1998	Finland	Q	Diagnosed asthma	Population registry	1713	16	3.9%	65-79%
Skadhauge, Christensen et al 1999	Denmark	Q	Ever asthma	Population registry	11688	12-41	6.2%	73%
Koeppen-Schomerus, Stevenson & Plomin 2001	United Kingdom	Q	Diagnosed asthma	Population registry	4910	4	18.4%	68%

Q=questionnaire RL= Record Linkage

Despite the encouraging progress to date, the search for specific asthma genes is still ongoing. Further study of the genes related to asthma is needed, particularly on how the genes work individually and in relation to the biological pathways implicated in the pathogenesis of asthma.

"New" risk factors – The so called "new" risk factors involved in the aetiology of asthma are thought to play a role in "setting off" or programming the initial susceptibility to sensitisation. These include various prenatal and perinatal exposures (or lack of exposures) to certain substances in the early years of life that may make the infant more susceptible to subsequently developing asthma or atopy. These issues are currently extensively studied and it is expected that within the next few years the role of these factors will add to our existing knowledge of the causes of asthma.

Prenatal and Perinatal factors – There is a general consensus that several pre- and perinatal factors are involved in the development of atopic diseases and asthma (Annesi-Maesano, Moreau, & Strachan, 2001; Warner, Jones, Jones, & Warner, 2000). Maternal –and thereby foetal - exposures to infections and various allergens during the course of pregnancy have been related to the subsequent development of allergic symptoms in children (Warner & Warner, 2000; McKeever, Lewis, Smith, & Hubbard, 2002). Low birth weight, premature birth and complications associated with assisted ventilation during the neonatal period are linked to non-optimal development of the lungs and impaired respiratory function. Although findings have supported a connection between prematurity, low birth weight and asthma, the evidence is not conclusive. In a study of singletons low birth weight was found to be associated with asthma in adolescence (Svanes, Omenaas, Heuch, Irgens, & Gulsvik, 1998), but the story may be different for multiple births. A Finnish study of adolescent twins found no significant

relationship between low birth weight, prematurity and the subsequent development of asthma (Rasanen et al., 2000).

Another factor which has been implicated in the aetiology of asthma is breast feeding. There has been some evidence that children who were exclusively breastfed for a period of at least four months were less likely to suffer from asthma at age 6 years (Oddy et al., 1999). However, more recent findings contradict this potentially protective effect of breastfeeding against asthma and suggest that it might even increase the risk for developing asthma (Sears et al., 2002; Takemura et al., 2001).

The Hygiene Hypothesis – The so called "hygiene hypothesis" suggested that childhood infections play a role in preventing atopic disorders (Strachan, 1989). Since the introduction of antibiotics and vaccinations, along with improved hygiene, and better socioeconomic conditions, the incidence of childhood infections has decreased. In contrast, atopic diseases such as asthma are increasing in prevalence possibly because the immune system is not being sufficiently challenged during the early years. For instance, day care attendance, a proxy measure for infectious disease in childhood, appears to lower the risk of childhood asthma (Ball et al., 2000; Infante-Rivard, Amre, Gautrin, & Malo, 2001). In addition, living in a large family, having older siblings and growing up in a farm environment are thought to protect from developing atopy related disorders (Leynaert et al., 2001; Riedler et al., 2001; Ball et al., 2000).

Although the hygiene hypothesis and the associated environmental factors are plausible explanations for the rising trend in asthma, little is known of how these factors are linked to disease expression.

2.2.1.3 Psychological implications

In addition to the physiological consequences of having asthma, there is some indication that asthmatic children are less well behaviourally adjusted than

healthy children. A number of studies have suggested higher rates of psychological difficulties in asthmatic children, especially regarding internalising behaviours (i.e. depressed mood, increased anxiety, being more withdrawn) (Mrazek, Schuman, & Klinnert, 1998a; Klinnert, McQuaid, McCormick, Adinoff, & Bryant, 2000). There is also some indication that asthma severity may be linked with greater behavioural difficulties (McQuaid, Kopel, & Nassau, 2001).

2.2.2 Eczema (Atopic Dermatitis)

Atopic dermatitis, also known as eczema, is a common chronic skin disorder with its onset during childhood. In developed countries, one in ten children suffers from this condition and the incidence is increasing (Barnetson & Rogers, 2002). The terms 'eczema' and 'atopic dermatitis' are often used interchangeably to describe an inflammatory process of the skin that is characterised by scaly and itching skin rashes. This chronic itching (*pruritus*) is a central aspect of the disease and is frequently accompanied by damage to the skin (i.e. cracking, bleeding, and infection) as well as sleep disturbance.

In infancy, the condition tends to appear on the face especially on the cheeks, whereas in later childhood and adulthood the affected areas tend to be the outer aspects of the limbs as well as the skin folds. Eczema is usually the first manifestation of atopy and about half of affected children subsequently develop other atopic disorders such as food allergy, asthma or allergic rhinitis (Barnetson et al., 2002; Gustafsson, Sjoberg, & Foucard, 2000). Atopic dermatitis develops early in life and 60% of cases present symptoms before the age of 5 years (Moreno Gimenez, 2000). Epidemiological studies suggest that in 60-70% of affected children the eczema clears or disappears completely by early adolescence (Charman, 1999; Williams, 2000). Eczema is most likely to persist

into adulthood when the infantile form of the disease was severe (Jaffe, 2000; Lammintausta & Kalimo, 1993). Later onset is rarely observed in adulthood.

2.2.2.1 Prevalence

Like other atopic disorders, the prevalence of eczema has increased substantially over the second half of the last century. Before the 1960s prevalence estimates for eczema in school children were between 2-3% and increased to 4-8% in the 1960s and to 9-12% during the 1970s (Larsen & Hanifin, 1992). The current global prevalence of eczema in children is 7.5% (ISAAC, 1998). However, there are considerable regional differences between and within countries ranging from 0.3 % to 20.5% prevalence (ISAAC, 1998).

In Britain 15-20% of schoolchildren and 2-3% of adults are affected by eczema (Charman, 1999). The British General Practice morbidity statistics provide further support for the rising trend of this condition in the UK. These reports indicate a four-fold increase of the consultation rates for eczema between the 1970s and the 1990s (OPCS, 1974; OPCS, 1995). In respect to sex differences, eczema tends to occur somewhat more frequently in females than in males (Kuster, Petersen, Christophers, Goos, & Sterry, 1990; Moreno Gimenez, 2000; Williams, 2000).

The reasons for the rising trend of eczema over the past decades remain poorly understood. In some cases, allergic reactions are responsible for the expression of the disease, whereas in other instances eczema breaks out in response to factors that are not associated with other allergic reactions. It has therefore been suggested that different subtypes of eczema exist, such as intrinsic or extrinsic, chronic or intermittent, as well as a combination of subtypes which are thought to co-occur with other atopic disorders (Williams, 2000).

2.2.2.2 Risk factors

Several risk factors have been implicated in the aetiology of eczema.

Genetics – Evidence for the importance of genetic factors in the development of eczema comes from family and twin studies. There is a strong familial component for atopic dermatitis – between 70-85% of patients with eczema have a family history of the condition (Kuster et al., 1990). Twin studies have also reported high heritability for eczema in children as well as in adolescents and adults (see Table 2.2).

Two studies from the Danish Twin Registry based on retrospective self reports of eczema during childhood (Schultz Larsen, Holm, & Henningsen, 1986; Schultz Larsen, 1993) found that in over 80% of cases eczema began before the age of 7 years. Furthermore, there was a substantial difference in probandwise twin concordances for eczema: 72% of cases MZ twins were concordant compared to 23% of DZ twins. Between 80 and 86% of the variance of eczema susceptibility was explained by genetic factors. Similarly, a Swedish study of school aged twins reported heritability for eczema of over 70% (Lichtenstein & Svartengren, 1997).

In adulthood the story remains virtually the same: the impact of genetic factors on eczema remains substantial but somewhat lower than in childhood. In the second largest twin study of allergy, Edfors-Lubs (Edfors-Lubs, 1971) reported a heritability of 61% for self reported eczema in a large population of adult twins. In line with this finding, genetic factors explained over 60% of the variance in a clinically recruited twin sample from the UK more recently (Mikkilinenil, Strachan, Snieder, Spector, & Bataille, 2001).

Table 2.2 Twin studies estimating the heritability of eczema

Study's author and year of publication	Country	Method	Definition	Population Source	$N_{(pairs)}$	Age (years)	Prevalence	heritability estimate
Edfors-Lubs, 1971	Sweden	Q	Self reported eczema	Population registry	6996	42-81	2.5%	62%
Schultz Larsen, 1986, 1993	Denmark	Q	Self reported Infantile eczema	Population registry	641	13-32	11.5%	80-86%
Lichtenstein & Svartengren 1997	Sweden	Q	Diagnosed or parent report	Population registry	1480	7-9	13.5%	71-74%
Mikkilinenil, Strachan et al 2001	United Kingdom	Q	Self reported eczema	Recruited registry	1546 (females)	18-79	--	61%

Q=questionnaire

As for other atopic disorders, the aetiology of eczema seems to depend strongly on genetic factors. It is likely that several genetic systems are involved, which may interact with specific environmental factors that remain to be identified.

Over the last few years, important advances on the molecular genetics of atopy have been made. Several genetic loci have been linked to atopic dermatitis, although results so far are not consistent. In a genome screen for susceptibility genes for atopic dermatitis, linkage was identified on chromosomes 1q21, 17q25 and 20p (Cookson et al., 2001). The findings further suggested that because these loci correspond to those associated with psoriasis, it is likely that the genes involved have general effects on skin inflammation and immunity. More recently, however, a Swedish study reported linkage on chromosomes 3, 13, 15, 17, and 18 (Bradley et al., 2002) and suggested that different qualitative phenotypes of atopic dermatitis (i.e. raised levels of IgE vs. IgE unrelated) correspond to different loci.

Social factors – The incidence of eczema has been found to vary with social status. For instance in the UK, significantly higher rates for atopic eczema have been found within the higher social classes (I and II) than in other social groups (Williams, Strachan, & Hay, 1994; Lewis & Britton, 1998; Harris et al., 2001). Corroborating this finding, a Swiss study found a similar relationship and reported a higher prevalence of eczema in social class I (9.1%) than in social class V (5.9%) (Wüthrich, 1996). This difference prevalence of eczema may be partly explained by environmental factors that are associated with lifestyle differences between social groups (Williams, 2000).

Unlike many other diseases, the incidence of eczema has been shown to be inversely related to family size even when controlling for other factors (Harris et al., 2001; Williams, 2000). A recent literature review found strong evidence for the protective effect of having more siblings in relation to atopic disorders (Karmaus &

Botezan, 2002) although the specific reasons responsible for this effect still need to be determined. A possible explanation for this protective 'sibling' effect might be the role of cross infection from siblings. Recent trends towards smaller family sizes, the increased use of antibiotics and improved hygiene may have reduced the opportunity for cross infection and therefore this may partly explain the rising trend in atopic disorders.

Food allergy – Hypersensitivity to certain foods, additives and preservatives has partly been linked to eczema. There is some evidence that the condition may be provoked or worsened by certain types of foods (Niggemann, 2002). There is no doubt that food allergy can act as a trigger for exacerbating eczema, but not all children with eczema are allergic to foods (Sicherer & Sampson, 1999). It is therefore likely that it only applies to a subgroup of children with a combination of food allergy and atopic eczema. It has been suggested that fewer than 10% of all children with atopic eczema are also allergic to certain foods (Barnetson et al., 2002). For those children with food related eczema the avoidance of provocative food might be an important step towards prevention (i.e. food resembling a shared environmental factor during childhood). However, the association between eczema and food allergy is complex and the mechanisms involved are as yet unclear (Niggemann, 2002).

Breastfeeding – Controversy remains regarding the prophylactic role of breastfeeding in the aetiology of atopic disorders in general and in eczema in particular. There is some evidence that breast feeding acts as a protective factor in the development of eczema, particularly for at-risk children with a family history of atopic disorders (see Gdalevich, Mimouni, David, & Mimouni, 2001) for a systematic review). In contrast, recent findings suggest the opposite and report a positive relationship between breastfeeding and eczema (Golding, Emmett, & Rogers, 1997; Bergmann et al., 2002; Kramer & Kakuma, 2002).

Inhaled allergens – While animal dander and various kinds of pollen have been implicated in the aetiology of eczema exacerbations, house dust mite allergens are probably one of the most important inhalant allergens (Arshad, Tariq, Matthews, & Hakim, 2001). House dust mite allergens are thought to be a major factor due to their large occurrence in the household, especially in carpets and bedding. Some findings suggests that a reduction of mite allergens in the home or environments free of house dust mites can be beneficial to sufferers of eczema (McNally, Williams, & Phillips, 2001; Friedmann & Tan, 1998). However, the effects tend to be temporary and a review of clinical trials on the prevention and treatment of atopic eczema found no conclusive evidence for the role of mite allergen reduction (Hoare, Li Wan Po, & Williams, 2000).

Psychosocial Implications – Eczema can be a distressing condition influencing children's daily lives, their personal and educational development and general well-being. The prolonged process of coping with a chronic disease, can be distressing for both the affected child and the family, and a worsening of eczema has been associated with emotionally stressful events (Picardi & Abeni, 2001; Kilpelainen et al., 2002). Through its physical appearance on the skin, eczema is – unlike asthma or hay fever – a visible and stigmatising disorder with potential psychosocial implications. Considering that the condition predominantly occurs during infancy and childhood, it coincides with critical periods of emotional and social development for the child. The disease may put restrictions on the types of activities the child can engage in (e.g. sports, swimming or contact with animals). Having eczema may also negatively affect self-image and increase self-consciousness. The effects of eczema can lead to social isolation and especially for severe cases there is a higher risk for the development of psychological and behaviour problems (Daud, Garralda, & David, 1993; Absolon, Cottrell, Eldrige, & Glover, 1997).

2.2.3 Comorbidity of Atopic Disorders

The three most common atopic conditions, asthma, hay fever and eczema show a similar hereditary background. It has been shown that the three disorders are highly correlated (ISAAC, 1998), although they do not always co-occur. For example countries with a high prevalence for one atopic disorder do not necessarily show a high prevalence for other atopies (ISAAC, 1998). This might be due to the fact that not all forms of asthma and eczema are mediated by a shared allergic response. It is possible that slightly different combinations of predisposing environmental factors trigger individual atopic disorders.

2.3 Overweight and Obesity

Overweight and obesity are chronic, metabolic conditions caused by many complex inherited and acquired factors, which include excessive caloric and food intake, insufficient physical activity, and genetic influences. The result is excess body fat which is stored due to an imbalance between energy intake and energy release. Obesity is a known risk factor for chronic diseases including heart disease, diabetes, high blood pressure, stroke and some forms of cancer. One widely used medical standard used to identify overweight and obese individuals is the body mass index (BMI). The BMI is calculated by dividing a person's weight in kilograms by their height in meters squared. The general cut off points in adults for defining overweight and obesity are 25-30 for overweight and over 30 for obesity.

2.3.1 Prevalence

The growing epidemic of obesity, with its attendant co-morbidities – hypertension, heart disease, stroke and diabetes - is a problem that is not limited to affluent western societies. The most recent data from the World Health Organisation (WHO) suggest that in the year 2000, more than half of the total

population of obese adults worldwide were from developing countries and economies in transition (World Health Organization, 2003). The situation for children and adolescents is equally worrying as the prevalence of overweight among this group has been increasing rapidly over the last twenty years with a tendency which is still on the rise (De Onis & Blössner, 2000; Chinn & Rona, 2001; Bundred, Kitchiner, & Buchan, 2001).

In the UK, according to the most recent health survey, 33% of women and 44% of men were considered overweight and 21% of women and 19% of men were classified as obese (Office for National Statistics, 2002a).

The incidence of overweight and obesity increases throughout childhood. For overweight, the prevalence for preschool children in the UK is 2.9% (De Onis et al., 2000). In older children (aged 7-11 years) this rate increases to 10.8% in boys and 16.0% in girls (Chinn et al., 2001). Similarly for obesity, the prevalence in this age group has increased more than two fold from 1.0% in 1984 to 2.2% in 1994 (Chinn et al., 2001). At age fifteen 31% of UK teenagers were overweight and 17% were obese (Reilly & Dorosty, 1999)

2.3.2 Risk Factors

Overweight and obesity are thought to be related to a number of interacting biological and social risk factors and theories relating to the aetiology of overweight and obesity include both physiological and behavioural explanations.

Genetics – Findings from twin, adoption and family studies provide strong evidence for the contribution of genetic factors in the pathogenesis of obesity (Maes, Neale, & Eaves, 1997).

The following table (Table 2.3) shows some of the published results from twin studies which suggest that between 50-84% of the variance in body weight and BMI are accounted for by genetic factors. In addition, shared environmental

effects appear to be largely absent. These similar estimates across different study designs suggest that genetic factors play a significant role in causing individual differences in body weight and that non-shared rather than shared environmental factors are important.

Table 2.3 Twin studies estimating the heritability of body weight and obesity

Study's author & year of publication	country	Method and Assessment	Measure	Population source	N(pairs)	Age (years)	heritability estimate	Shared environment
Wilson, 1976	USA	Measured body weight	Body weight	Recruited sample	233-242	1-3	68%*	20%*
Wilson, 1979	USA	Measured body weight and height	Body weight	Recruited sample	n/a	5-8	76%*	10%*
Stunkard, Foch & Hrubec 1986	USA	Reported body weight and height	BMI	Recruited sample	4071	20 45	77% 84%	0%
Stunkard, Harris et al 1990	Sweden	measured	BMI	Twins reared together and apart	93 MZA 154 MZT 218 DZA 208 DZT	21-80	69-74%	0%
Allison, Kaprio et al 1996	USA, Japan, Finland	measured	BMI	Recruited twins reared apart	53 MZA	n/a	50-70%	n/a
Pietilainen, Kaprio et al 1999	Finland	Reported body weight and height	BMI	Population registry	4884	16-17	80%	0%
Faith, Pietrobelli et al 1999	USA	measured	Percent body fat	Clinical recruited	66	3-17	75-80	0%
Koeppen-Schomerus, Wardle & Plomin 2001	United Kingdom	reported body weight and height	Body weight corrected for height	Population registry	3636	4	62% weight 59% overweight	25% weight 26% overweight

n/a = details not available
* estimates based on correlational data

Genetic factors are also likely to be involved in influencing appetite regulation, resting metabolic rate as well as food preferences. One of the most promising candidates was the hormone leptin which was first discovered in 1994 in a study of obesity using mice (Zhang et al., 1994). Subsequently the human Ob gene was mapped onto chromosome 7 (Green et al., 1995). Leptin which is produced by the adipocytes (fat cells), is thought to be involved in the monitoring of lipid levels that control food intake: As the amount of fat stored in the adipocytes rises, leptin is released into the blood stream in proportion to body fat mass signalling to the brain when the body has sufficient nourishment (Zhang et al., 1994). In overweight and obese people high levels of leptin have been found leading to the hypothesis that obese and overweight people may be insensitive to leptin. However, current knowledge suggests that while leptin is an important factor, it is likely that there are also other molecules involved in the regulation of body weight by affecting feelings of satiety. Although leptin is one of the most prominent examples, numerous other proteins and neuropeptides that are involved in the regulation of food intake and energy expenditure have also been identified in recent years.

Despite notable advances in the molecular genetics of rare single-gene causes of human obesity, it is unlikely that the heritability of obesity is due to single gene disorders alone. In fact, genes associated with obesity related phenotypes in humans have been found on all chromosomes. The most recent report on the human obesity gene map shows an embarrassment of riches, with more than 300 genes associated with obesity, although as is the case with other complex disorders, failures to replicate are common (Chagnon et al., 2003).

The ongoing search for obesity genes should not only result in a better understanding of energy metabolism, but also aid the development of new strategies for treatment.

The continued interest in both the environmental and genetic contributors towards the development of overweight and obesity suggests the timeliness of research on this major health problem.

Resting Metabolic Rate – It has been argued that lower rates of metabolism may be associated with obesity because a lower metabolic rate would imply less energy expenditure and hence a lower amount of calories needed during resting periods to maintain vital bodily functions (Goran, 2000).

Although there has been some support for lower metabolic rates in obese individuals, there is conflicting evidence as other studies found that resting metabolic rates to be higher in obese individuals (Astrup, 1996). Another theory explains this discrepancy by suggesting that obese people have a lower resting metabolic rate initially but once substantial amounts of weight have been gained the bulk of the excessive weight then triggers the rise in metabolic rate (Ravussin & Bogardus, 1989). Twin and family studies suggest that for resting metabolic rate heritability estimates 40% (Bouchard, 1990).

Changes in Diet and Energy intake – Dietary changes as well as trends in energy value are important factors in the aetiology of obesity. In contrast to the increasing rates of overweight and obesity in Britain over the last 30 years, energy intakes have actually declined. For example in the year 2000, the average energy intake was 1,750 kcal per person per day, compared to 2,290 kcal in 1975 (Department for Environment, 2000). There has also been a change in the composition of people's diet, i.e. the contribution of fat, protein and carbohydrate. Since the mid 1980s the post-war trend of increased consumption of fat has been reversed, concomitantly, the proportion of carbohydrate towards peoples' diet has been increasing while the contribution of protein remained fairly stable (Department for Environment, 2000). Despite a reduction in daily caloric intake

and moving away from a diet high in fat, the rates of overweight and obesity continue to rise.

Although diet is an important aspect in the aetiology of overweight and obesity, it cannot account for the rising trend on its own. Dietary factors can account for changes in relation to the population mean increase of weight; however, the question remains *whether* and *how* nutritional changes over time relate to individual differences in overweight and obesity.

Physical Exercise – The increase in prevalence of obesity also coincides with a decrease of daily energy expenditure. In western societies, the amount of physically intense activities at home and at the workplace has fallen over the last centuries due to modernisation and technological advances, for instance due to the increasing use of motorised transport and electrical appliances (Office for National Statistics, 2002a). A shift has taken place from an agricultural to an industrialised and now an information economy. In addition to the fact that today fewer jobs require strenuous physical labour, many people's leisure time tends to be dominated by activities requiring little or no physical effort. According to the most recent national household survey, watching TV is one of the most popular home-based activities in Britain (Office for National Statistics, 2002a). In 1975 the average time spent watching TV was 14 hours per week (Central Statistical Office, 1975), whereas today on average 20 hours per week are spend watching television (Office for National Statistics, 2002b). In addition, the increasing trend towards physical inactivity is reflected by the rising sales and popularity of computer games, DVDs and videos, especially by children (Office for National Statistics, 2002a).

It is very likely that physical inactivity is a substantial contributor towards the average increase of weight in many Western countries. However, at present

little is known as of the effects of physical activity patterns on individual differences in weight.

In conclusion, there is strong evidence for the involvement of genetic factors on body weight. However, it is presently still unclear which genetic mechanisms are involved and how they are regulated. As the genetic mutation rate is very low, the increase of obesity and overweight in the population is likely due to drastic changes in environments and lifestyles over the last century. The rising trend in obesity is likely to be explained by an interaction of genetic factors with changes in the environment that lead to the manifestation of the condition in those susceptible.

2.4 Otitis Media

Otitis media refers to two inflammatory conditions of the middle ear. In acute otitis media (AOM) symptoms of acute illness can be observed which are often preceded by a cold or infection. AOM is characterised by a rapid onset usually following viral upper respiratory tract infection; symptoms include earache and fever. The chronic form of OM, otitis media with effusion (OME), is characterised by the presence of fluid in the middle ear. This fluid causes immobility of the tympanic membrane and often involves diminished hearing and sometimes conductive hearing loss. OME can also be caused by blockage of the eustachian tube without the development of bacterial or viral infection. Episodes of AOM, especially during the early years, are frequently followed by OME, which may persist for several weeks to months. It is estimated that about one-third of all upper respiratory tract infections develop into OM in young children (Daly, 1991).

2.4.1 Prevalence

Otitis media tends to begin early in life. However, the frequency increases and peaks between 6 and 18 months and it has been suggested that over 30% of

children will have experienced at least one episode of OM before the age of 2 years (Faden, Duffy, & Boeve, 1998). The prevalence rate tends to be higher among urban populations than suburban or rural populations (Paradise et al., 1997). Although AOM accounts for the majority of episodes in childhood, OME constitutes a greater proportion of the episodes earlier in infancy (Faden et al., 1998).

2.4.2 Risk factors

It has long been recognised that OM is a complex disease with numerous environmental and infectious aetiologies. Several environmental factors have been proposed as risk factors for OM such as non-optimal housing conditions, low socioeconomic status, day-care attendance and exposure to tobacco smoke.

Tobacco smoke – Exposure to tobacco smoke in the household is thought to have an impact on the development and persistence of OM, especially when the exposure is persistent and takes place early in life (Froom et al., 2001; Gryczynska, Kobos, & Zakrzewska, 1999; Uhari, Mantysaari, & Niemela, 1996).

Social factors and family size – In contrast to the risk factors associated with atopic disorders, both day care attendance and a high number of siblings are thought to increase the occurrence of OM in young children (Dewey, Midgeley, Maw, & The ALSPAC Study Team, 2000; Paradise et al., 1997). The increased susceptibility is likely to be related to respiratory infections that are passed on between siblings as well as other children.

Lower socioeconomic status also contributes to the risk of developing OM, suggesting that environmental factors in the home may be important contributors towards the risk of developing OM.

Genetics– There is accumulating evidence that susceptibility to recurrent episodes of acute otitis media as well as persistent OM with effusion is largely determined by genes. Recent twin studies have consistently shown that genetic

influences contribute strongly to OM risk (Kvaerner, Tambs, Harris, & Magnus, 1997; Casselbrant et al., 1999; Rovers, Haggard, Gannon, Koeppen-Schomerus, & Plomin, 2002). These studies summarised in the following table (Table 2.4) have reported heritability estimates for OM between 45% and 73%.

It is likely that the genetics of OM are complex and although the physiological aspects involved in the expression of the disease are well understood, there are as yet no susceptibility genes that have been specifically linked to OM.

Table 2.4 Twin studies estimating the heritability of otitis media

Study's author & year of publication	Country	Method and Assessment	Definition	Population source	N	Age (years)	Prevalence	heritability	shared environment
Kvaerner, Tambs et al 1997	Norway	Q	self report	Population registry	2750	2-7	8.9%	74% (females) 45% (males)	ns (females) 29% (males)
Casselbrant, Mandel et al 1999	USA	Otoscopic assessments	diagnosed	Recruited clinical	140	2	--	73%	ns
Rovers, Haggard et al 2002	UK	Q	parent report	Population registry	1373	2 3 4	--	49% 66% 71%	41% 22% 16%

Q=questionnaire; ns=not significant

2.4.3 Developmental implications

Persistent or recurring bouts of OM accompanied by some degree of hearing impairment during the early years may have long-term effects on early communication and language abilities, auditory processing, psychosocial and cognitive development, and subsequent educational progress (Abraham, Wallace, & Gravel, 1996; Paradise et al., 2000; Shriberg, Friel-Patti, Flipsen, Jr., & Brown, 2000; Vernon-Feagans, Manlove, & Volling, 1996) with sequelae possibly continuing into the teenage years (Bennett, Haggard, Silva, & Stewart, 2001). More research on the long-term effects of OM is needed, however, because other studies have reported weak or no links between early life OM and developmental deficits (Peters, Grievink, van Bon, van den Bercken, & Schilder, 1997; Feldman et al., 1999; Augustsson & Engstand, 2001).

2.5 Summary

All of the disorders described in this chapter have become increasingly more prevalent during the last century. Epidemiological and environmental research suggests that a vast number of environmental risk factors may be able to explain the rising trend of many disorders. In addition, evidence from twin, family and adoption studies suggests that all of the described disorders are substantially influenced by genetic factors. Because the rapid increase cannot be accounted for by genetic factors alone, it is likely that environmental changes are responsible. Although changes of environmental conditions can explain average population increases of some disorders, they tell us little about disease aetiology. At present, the mechanisms by which these disorders are become expressed are still largely unknown.

3 Twin Studies and Methodology

3.1 Overview:

This chapter gives a brief description of quantitative behavioural genetic methods, with primary focus on twin studies. The main assumptions and limitations of the methodologies are summarised.

3.2 The Classical Twin Design:

The twin method is a quasi-experimental design that compares the resemblance between monozygotic (MZ) twins, who are genetically identical because they derive from the same fertilised egg, and dizygotic (DZ) twins, who share on average 50 per cent of their genes and derive from two separately fertilised eggs. Half of DZ twin pairs are the same sex and half are opposite sex, whereas MZ twins are always the same sex.

The different levels of genetic relatedness between MZ and DZ twin types are used to assess the contributions of genetic and environmental factors to individual differences for any phenotype or trait. If a trait is influenced by genetic factors, MZ twins should resemble each other to a greater extent than DZ twins. A comparison of correlations between MZ and DZ twins may be used to estimate the relative size of genetic and environmental influences. Doubling the difference between the correlations for MZ and DZ twins provides a rough approximation to heritability, because MZ twins are twice as similar genetically as DZ twins. The remainder of phenotypic variance can be attributed to two types of environmental influence called *shared environment* which makes family members similar, and *non-shared environment* which makes family members different. Twin within-pair similarity for the

phenotype is assumed to be due to genetic factors plus common or shared environment factors. Shared environment can be estimated as the extent to which heritability is less than the MZ correlation. Non-shared or unique environment is a residual term that includes environmental factors that make family members different from each other and error of measurement.

Although twin correlations can provide a rough approximation of the direction of results, structural equation model-fitting analyses of variance/covariance matrices are formally used to estimate genetic and environmental parameters and to provide confidence intervals for these estimates (Neale & Cardon, 1992).

Figure 3.1: Univariate ACDE path model, representing additive genetic effects (A), shared environmental effects (C), non-shared environmental effects (E), dominance genetic effects (D) on phenotypes (TWIN 1 and TWIN 2 for first-born and second-born twin) measured in monozygotic (MZ) and dizygotic (DZ) twins reared together.
The genetic correlation (r_g) is fixed at 1.0 for MZ twins and 0.5 for DZ twins; the genetic dominance correlation (r_d) is fixed at 1.0 for MZ twins and 0.25 for DZ twins and the shared environmental correlation (r_c) is 1.0 for both zygosity groups. Nonshared environment is not correlated as it is unshared within twin pairs.

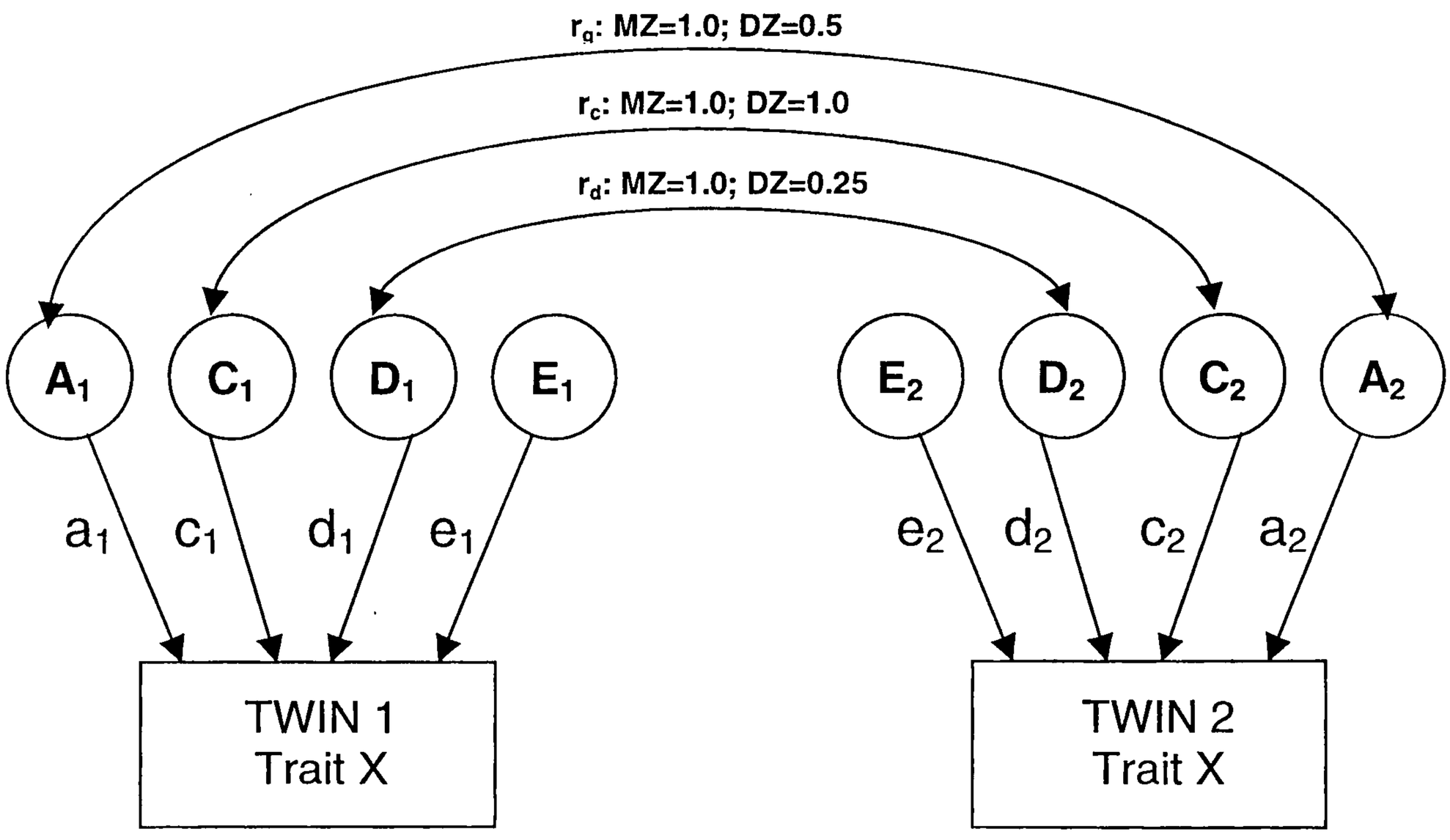


Figure 3.1 shows a path diagram for the classical twin study using MZ and same-sex DZ pairs raised within the same family. The latent factors (i.e. A, C, E, D) are represented by circles whereas measured variables are shown by squares and indicate the phenotypic trait under investigation for each twin. The causal paths (between the latent and observed variables) are represented by single headed arrows and the correlational paths (between the latent variables) are shown by double headed arrows. The possible causes of variation include additive genes (A), non-additive genes or dominance (D), common or shared environment (C) and non-shared or unique environment (E). Since the effects of shared environmental factors and genetic dominance are confounded, a full model including additive and dominance genetic factors and specific and shared environmental factors (ACED) cannot be tested. It is often apparent from the pattern of twin correlations whether an ACE or an ADE model should be applied to the data (e.g. if the DZ correlation is less than half of the MZ correlation it is likely that non-additive or dominance genetic effects are at work indicating the appropriateness of using an ADE model).

In the univariate ACE model the within-pair similarity for the phenotype is assumed to be due to additive genetic factors plus shared and non-shared environmental factors. In contrast, the ADE model decomposes the phenotypic variance into additive as well as non-additive genetic components. The remainder of the variance is accounted for by non-shared environmental effects.

The fit of structural equation models to the data can be assessed by several goodness-of-fit indices, details of which are provided in Appendix 2. Both models assume that gene-environment interactions or correlations, assortative mating, or zygosity-related variance differences are absent.

3.3 Assumptions and Considerations of the Twin Method

The twin method is based on a number of assumptions and methodological considerations, some of which are outlined below.

3.3.1 Equal Environments Assumption (EEA):

The equal environments assumption (EEA) assumes that MZ and DZ twins are experiencing similar types of environments regardless of their zygosity. If this assumption is violated and if MZ twins were experiencing a more similar environment in respect to the trait under investigation, their phenotypic similarities may also increase, and as a consequence genetic influences may be overestimated.

One possibility of assessing the EEA is to study the effect of perceived zygosity in misclassified twins. When twins, or their parents, think they are fraternal (DZ) when they are in fact identical (MZ), these misclassified twins have been found to be as similar behaviourally as MZ twins with correctly perceived zygosity (Kendler, Neale, Kessler, Heath, & Eaves, 1994; Xian et al., 2000).

Although most twin studies do not include a test of the EEA, it has generally been found to be reasonable for most traits (Bouchard, Jr. & Propping, 1993). In cases in which the equal-environments assumption has been tested empirically, the findings generally indicate that the environments are roughly the same for MZ and DZ twins (Cronk et al., 2002; Borkenau, Riemann, Angleitner, & Spinath, 2002).

3.3.2 Prenatal Environment

Another factor which could have implications for findings from twin studies is the effect of prenatal environment. It has been claimed that some types of MZ twins may experience more similar environments in utero (Prescott, Johnson R.C., & McArdle

J.J., 1999). For instance, two thirds of MZ twins share the same chorion ('monochorionic') whereas DZ twins are always in separate chorions ('dichorionic'). This chorionicity effect could potentially affect estimates of shared environment, i.e. inflating shared environmental estimates for monochorionic twins (only MZ) as opposed to dichorionic twins (mostly DZ).

On the other hand, it is also possible that MZ twins actually experience greater environmental differences prenatally, for example through greater intrauterine competition for nutrition. The resulting within-pair differences at birth can have implications for prenatal growth and organ maturation (e.g. twin to twin transfusion syndrome, a condition which affects only MZ twins) (Machin, 2001). Most studies that have attempted to directly test the association between chorionicity, placentation and development have reported small effects (Jacob et al., 2001; Gutknecht, Spitz, & Carlier, 1999; Sokol et al., 1995). However, because most studies are based on relatively small samples, the findings require replication. Hence, the debate surrounding the effect of chorionicity and placentation on complex traits remains at present unresolved.

3.3.3 Assortative Mating

Twin analyses are based on the assumption of random mate selection for the respective trait under investigation. Assortative mating occurs when mate selection is based on a particular phenotype such as education, shared cultural or environmental influences, or on choosing a genetically related partner. If a trait is affected by non-random mating, twin similarity in DZ twins for this trait will be increased and estimates of common environmental influences will be artificially inflated, while at the same time estimates of genetic effects will be reduced. In order to control for the effects of non-

random mating, the twin design can be extended to include phenotypic data for the parental generation (Neale et al., 1992).

3.3.4 Generalisability

The importance of twin studies is based on how their findings translate to those of non-twin populations. One issue concerns the representativeness of twin samples in relation to the general population.

Multiple pregnancies differ from singleton pregnancies because twins tend to be born on average about 2 weeks earlier and they can also be adversely affected by the different intrauterine conditions (Phillips, 1993). Furthermore, twins tend to be lighter at birth and typically weigh about one third less than singletons. This birthweight difference, however, tends to be only transient and generally disappears by mid-childhood (Wilson, 1979).

3.4 Gene-Environment Correlation (G-E)

Gene-environment correlations (G-E) assess the degree of association between genetic propensities of individual differences and environmental experiences or events (Kendler & Eaves, 1986). There are three types of G-E correlations: *passive* (i.e. family members share both genes and environments, and their environments are correlated with their genetic propensities), *active* (i.e. based on their genetic propensity individuals actively choose or seek out particular environments) and *evocative* (i.e. through their genetic make-up, individuals may evoke certain reactions from other people). In quantitative genetic analyses, G-E correlations are often estimated as part of the main effect for genetic influences (Plomin et al., 1997). Multivariate twin analyses can be a useful way to explore shared genetic risk factors between measures of the environment and developmental outcomes.

3.5 Gene Environment Interaction (GxE)

Genotype environment interaction (GxE) involves the study of genetic susceptibility or vulnerability to certain environments. In other words, it assesses the extent to which environmental effects on a phenotype differ as a function of the genotype.

A few examples have been found in which environmental stressors primarily affect individuals who are at genetic risk (Kendler et al., 1995; Heath, Eaves, & Martin, 1998). The twin design can be used to identify instances of GxE. One possible approach is to use one twin's phenotype as an index of genetic risk to explore interactions with measured environments. In addition, GxE interactions can be detected by twin designs that allow estimates of genetic and environmental influence to vary in different environments.

3.6 DeFries-Fulker Extremes Analysis

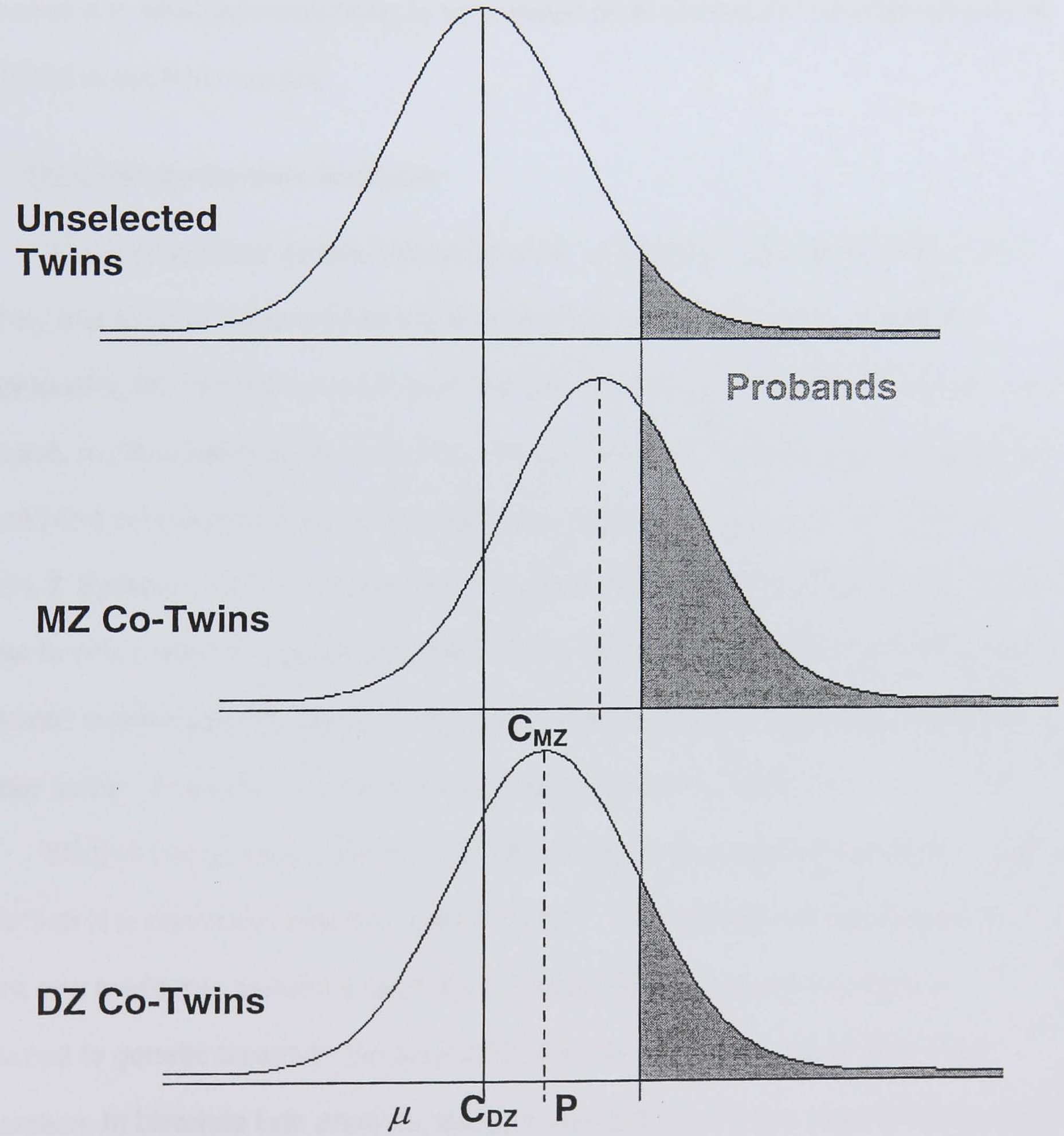
A quantitative genetic technique called DF extremes analysis (DeFries & Fulker, 1985; DeFries & Fulker, 1988) facilitates the assessment of the extent to which genetic and environmental factors that affect the extreme of the distribution also affect a measured quantitative trait throughout the distribution. Rather than merely assigning a dichotomous diagnosis, DF extremes analysis (DeFries et al., 1988) addresses the aetiology of the links between the normal and abnormal. DF extremes analysis is conceptually similar to the liability-threshold model (Falconer, 1965; Smith, 1974). An important difference between the two approaches is that the liability-threshold model assumes a continuous dimension even though a dichotomous disorder has been assessed. In contrast, DF extremes analysis assesses rather than assumes a continuum (Plomin, 1991).

The basic DF model is represented as the regression, $C = B_1P + B_2R + A$, in which the co-twin's score (C) is predicted from the proband's score (P) and the coefficient of relatedness (R), which is 1.0 for MZ and 0.5 for DZ pairs. Because the proband mean is transformed to a mean of 1.0 and the unselected population to a mean of 0.0, the mean of the co-twin's score for MZ and DZ twins estimates their 'group familiality.' The regression coefficient B_1 indicates the within-pair similarity independent of zygosity and the regression weight B_2 estimates 'group heritability'. Therefore 'group shared environment', that is twin resemblance not explained by genetic factors, can be estimated by subtracting group heritability from MZ group familiality.

As illustrated in Figure 3.2, the essence of DF extremes analysis is that if the mean difference between the probands and the population is due to genetic factors, the mean of co-twins of MZ probands will regress less far back to the population mean than that of co-twins of DZ probands. This difference is used to estimate what is called 'group heritability' to distinguish it from the usual heritability estimate which refers to differences between individuals rather than to mean differences between probands and the population. DF extremes analysis can yield evidence for genetic influence only to the extent that the quantitative trait is genetically linked to the disorder, that is, to the extent that the same genes affect the disorder and the dimension. However, showing group heritability for a quantitative trait measure and showing that group heritability is similar to the usual individual differences heritability does not unequivocally prove that the same genes are responsible for the disorder at the extreme and the dimension as a whole. For example, a rare genetic mutation with a major effect might be over-represented in the extreme group but account for little variation in the normal range.

Figure 3.2: *DF Extremes Analysis (DeFries & Fulker, 1985, 1988)*

This diagram shows hypothetical distributions of a trait in an unselected sample of twins and of the identical (MZ) and fraternal (DZ) co-twins of probands at the upper extreme. The proband mean is P. The differential regression of both the MZ and the DZ co-twin means (C_{MZ} and C_{MZ}) toward the mean of the unselected population (μ) provides a test of genetic influence. That is to the extent that being at the upper extreme in probands is heritable, the quantitative scores for MZ co-twins will be more similar to that of the probands than will the scores of the DZ co-twins. In other words, the mean of MZ co-twins will regress less far back toward the population mean than will that of DZ co-twins (adapted from Plomin, DeFries, et al. 2001).



3.7 Probandwise Concordance

The probandwise concordance (PC) is an index of the probability that the co-twin of a twin affected by a condition will also be affected. As with correlations, the relative magnitude of concordance rates for MZ and DZ pairs is indicative of genetic influence on a disorder. The probandwise concordance is calculated as the number of probands (i.e. affected individuals) in concordant pairs divided by the total number of probands in the total sample.

3.8 Multivariate Genetic Analysis

Many traits show genetic influence when studied individually. However, it is unlikely that each is influenced by exclusively different sets of genes. Instead of decomposing the variance of each trait into genetic and environmental components of variance, multivariate genetic analysis decomposes the covariance between traits into genetic and environmental components of covariance (Plomin et al., 2001; Eaves, Martin, & Eysenck, 1977). In other words, multivariate genetic analysis assesses the extent to which traits are genetically distinct (*genetic heterogeneity*) or whether there is genetic overlap (*genetic comorbidity*). Multivariate analyses assess the extent of genetic and/or environmental basis for association between variables.

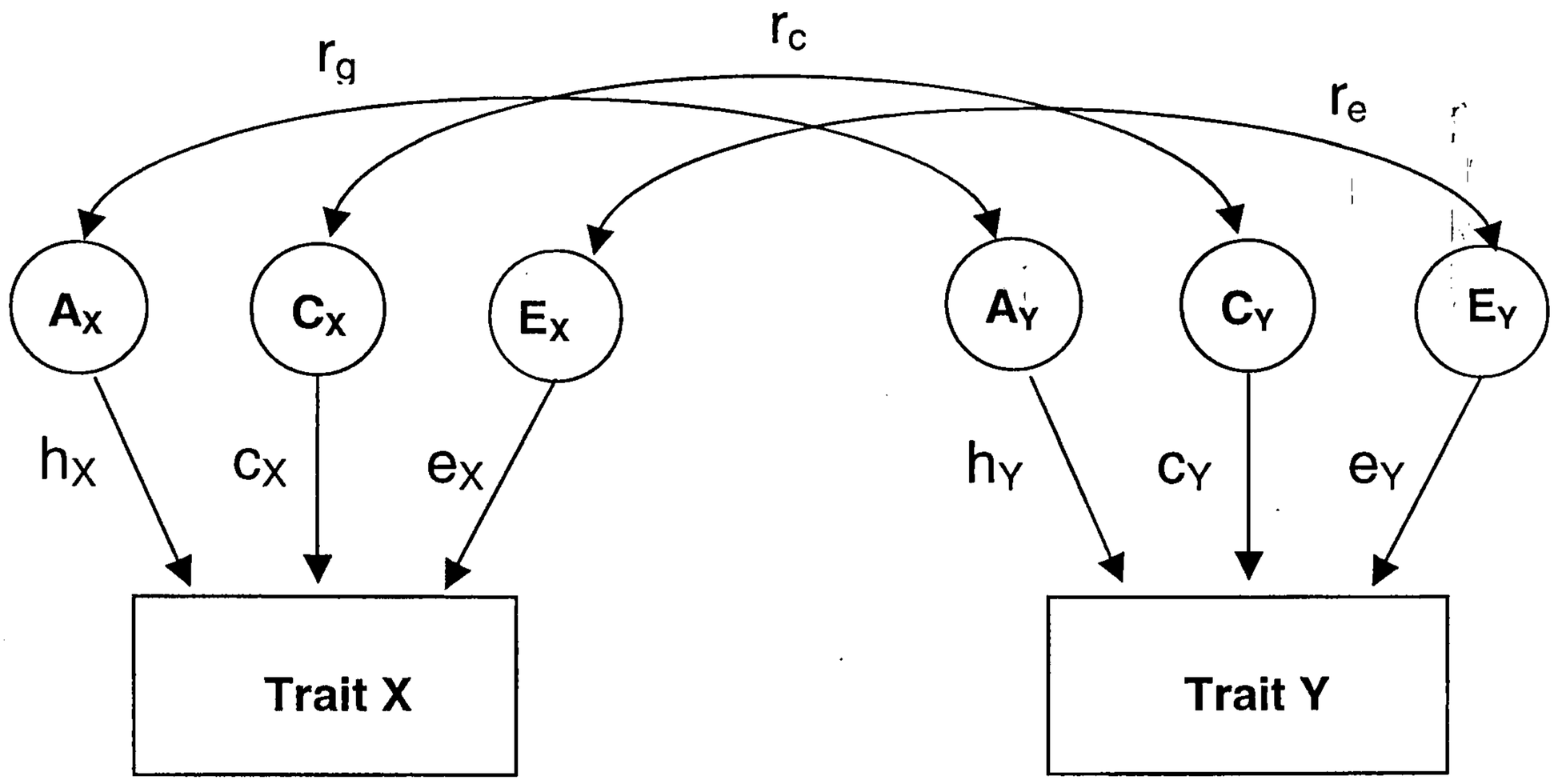
Multivariate genetic analysis is based on cross-twin correlations. That is, one twin's trait X is correlated with the co-twin's trait Y. In univariate twin analyses (i.e. where one twin's X is correlated with the co-twin's X) the variance of a trait is attributed to genetic factors to the extent that the MZ correlation exceeds the DZ correlation. In bivariate twin analysis, the covariance between two traits is attributed to genetic factors to the extent that the MZ cross-twin correlation exceeds the DZ cross-twin correlation.

3.8.1 Correlated Factors Model

A frequently applied model to explore multivariate relationships between two or more traits is called the correlated factors model (Loehlin, 1996), which assumes that the phenotypic correlation is mediated by correlated latent genetic and environmental factors. A diagram of the correlated factors model is shown in Fig. 3.3. Just as in the univariate model the covariance between twins is decomposed into genetic and environmental pathways, so the covariance between trait X and trait Y for the same individual is partitioned into genetic and environmentally mediated pathways. The genetic contribution to the phenotypic covariance is given by the pathway $\mathbf{a_x} \times \mathbf{r_g} \times \mathbf{a_x}$, where $\mathbf{r_g}$ is the genetic correlation. The genetic correlation represents the overlap between genetic influences on trait X and trait Y independent of their respective heritabilities. The shared environment and nonshared environment components of covariance are given by $\mathbf{c_x} \times \mathbf{r_c} \times \mathbf{c_y}$ and $\mathbf{e_x} \times \mathbf{r_e} \times \mathbf{e_y}$ where $\mathbf{r_c}$ and $\mathbf{r_e}$ are the shared environment correlation and the nonshared environment correlation.

The proportion of the phenotypic correlation mediated by shared genetic factors is called bivariate heritability and is given by dividing the genetic covariance by the phenotypic correlation. Similarly, estimates of bivariate shared environment are expressed as the shared environmental covariance over the corresponding phenotypic correlation.

Figure 3.3 Correlated factors model used for multivariate genetic analyses (the diagram shows one twin only)



A_X, A_Y = additive genetic factors;
C_X, C_Y =shared environmental influences;
E_X, E_Y = unique environmental influences;
h_X, h_Y, c_X, c_Y, e_X, e_Y= parameter estimates of genetic and environmental influences;
r_g = genetic correlation;
r_c = shared environmental correlation;
r_e=non-shared environmental correlation.

4 Aims

4.1 Study Context

Although heritability has been assessed for several phenotypes related to health in adults, few studies to date have attempted to explore the onset and early stages of common disorders in children and their implications to development employing a genetically informative design. Twins offer a unique opportunity to study the development of a disease from a genetic and environmental perspective. The aims of this thesis are to assess the contributions of genetic and environmental effects to four medical disorders (i.e. asthma, eczema, overweight and otitis media, see Chapter 2), and to explore their potential links with behavioural development.

4.2 Research Scope

The studies that will be described in the following sections are based on the Twins' Early Development Study (TEDS), a large representative UK sample of twins born in 1994 to 1996. An overview of the analyses that follow is provided below. In the next chapter, *Study Design and Procedures*, details of the study's background, samples and measures are given. The final chapter of this dissertation includes a summary of the main results, their implications and general conclusions.

4.2.1 *Chapter 6* Asthma

Although the genetic and environmental factors of asthma have been investigated later in life, few studies have focused on the early development of asthma. The aim of this study is to assess the contributions of genetic and environmental factors towards asthma in childhood and to investigate whether

there is evidence for developmental differences and/or associations between asthmatic and non-asthmatic children.

4.2.2 *Chapter 7* Eczema

Eczema is a condition with early onset which occurs often in early childhood. The aim of the present study is to assess the genetic and environmental contributions towards eczema liability within a sample of young twins. In addition, developmental associations between eczema status and assessments of cognition, language and behaviour problems will be explored.

4.2.3 *Chapter 8* Weight and Overweight

Previous twin and adoption studies have documented genetic influences on individual differences in weight. Much less, however, is known about the genetic influences on overweight, especially during childhood. The aim of this study is to assess the genetic and environmental influences on weight within the normal range as well as on overweight.

Early eating experiences may contribute to overweight and obesity. The relationship between parent feeding behaviours and children's weight will be explored in respect to group differences and correlational associations. In addition, developmental differences and associations between normal weight and overweight children will be evaluated for language, cognitive ability and behaviour problems.

4.2.4 *Chapter 9* Otitis Media

A number of environmental risk factors have been linked to otitis media (OM), but findings from twin and family studies suggest substantial influence of genetic factors.

In this chapter, the genetic and environmental contributions of otitis media (OM) will be studied. In addition, the relationship of OM with development will be

investigated for language development, non-verbal cognitive ability and behaviour problems from age 2 to 4 years.

5 Study Design and Procedures

5.1 Overview

The aim of the current study was to assess in a large population sample of UK twins the contributions of genetic and environmental factors to the variance of the health related phenotypes that have been described in Chapter 2 and their relationship with developmental outcome.

The present chapter provides some general details on the Twins Early Development study, its design, the measures that are included, its scope and a description of the sample.

5.2 The Twins Early Development Study (TEDS)

5.2.1 Background and set-up

The Twins Early Development Study (TEDS; Trouton, Spinath, & Plomin, 2002) was launched in 1995 and is funded by a programme grant from the Medical Research Council (MRC, UK). The primary research focus of TEDS is the genetic and environmental investigation of the early emergence and persistence of language difficulties and their links to other problems such as cognitive development and behaviour problems (Dale et al., 1998; Eley et al., 1999; Purcell et al., 2001; Plomin, Price, Eley, Dale, & Stevenson, 2002). In addition, TEDS provides a valuable resource for exploring other areas of research (e.g. anxiety, depression and hyperactivity) and since the start of the study, several spin-off projects have emerged.

Initially, with the assistance of the Office for National Statistics (ONS), the families of all twins born in 1994, 1995 and 1996 in England and Wales were contacted by post and invited to take part in TEDS. Parents who responded and expressed an interest in participating in the study were sent a letter of invitation and a

questionnaire booklet ('Welcome to TEDS!') when the twins were about 18 months old. This booklet contained questions on family background and will subsequently be referred to as 'background' booklet.

Parents of twins born in 1994 and 1995 were told that TEDS would contact them again around their twins' second birthday to ask them to play a few games with their twins and to answer a few questions about the twins as well as their family. Further questionnaire packs were sent to these families before their twins' third and fourth birthdays. These questionnaire booklets are referred to here as the 2-year, 3-year, and 4-year booklets. Families of twins born in 1996 were only asked to complete the background and the 4-year booklet.

5.2.2 Sample Description

The sampling frame consisted of the entire population cohort of twins born in England and Wales between 1994 and 1996. Families with twins born during these years were identified and contacted by ONS. A total of 16,810 families returned a postcard agreeing to participate. These families were sent a family background booklet asking for family details followed by questionnaire booklets which were sent at the time of the twins' second, third and fourth birthdays. At each stage of the study, written consent was obtained from the twins' parents who were told that they could withdraw from the study at any time. For more than 97% of TEDS families, the questionnaire and assessment booklets were completed by the mothers.

For the current analyses, details were available from 13,428 families who completed the background booklet, 6,163 families who completed the 2-year booklet, 5,999 families who completed the booklet at age 3, and 7,202 families who completed the booklet at age 4 years. A total of 3,910 families completed all booklets.

Families were excluded in which one or other twin had severe perinatal problems (298 families) or severe medical or genetic problems (278 families).

The zygosity of the twins was diagnosed by parental ratings of physical similarity from the background booklets and the 3-year booklets. A comparison of the parent zygosity ratings between the background and the 3-year booklets showed a high degree of stability. Zygosity was correctly assigned by parent ratings with over 94% accuracy as validated against zygosity assigned by identity of polymorphic DNA markers (Price et al., 2000). For 350 families twin zygosity could not be determined and these twin pairs were therefore excluded from the analyses.

The final target sample consisted of 9,025 families who returned the background booklet and at least one other booklet. This sample included 1,428 pairs of monozygotic (MZ) males, 1,649 pairs of monozygotic (MZ) females, 1,499 pairs of dizygotic (DZ) males, 1,498 pairs of dizygotic (DZ) females, and 2,951 dizygotic opposite-sex (DZOS) pairs.

5.2.3 Demographic characteristics

Despite the attrition, it has been demonstrated that the TEDS sample is reasonably representative of the UK population of parents of young children in terms of parental ethnicity, education, and employment status (Dale et al., 1998). Representativeness was ascertained by comparing the sample to 1994 UK census data from the Office for National Statistics (see Table 5.1).

Table 5.1 Representativeness of the TEDS sample compared to the UK general population based on data from the General Household Survey (GHS).

	***UK*[1]**	***TEDS sample***		
		***Total*[2]**	***Complete*[3]**	***Target*[4]**
Children are white	93%[5]	92%	94%	93%
Mother has A-levels	32%[6]	35%	39%	37%
Mother without formal qualifications	19%[7]	10%	7%	8%
Father without formal qualifications	16%[8]	14%	12%	12%
Mother is employed full-time	49%[9]	42%	42%	43%
Father is employed full-time	89%[10]	91%	93%	92%

[1] data from the General Household Survey (GHS; Great Britain Office of Population Censuses and Surveys, 1996).
[2] TEDS families who completed the first contact booklet (N = 13,428).
[3] TEDS families who completed booklets at all measurement occasions (N = 3,910).
[4] TEDS families who completed the first contact booklet and at least one questionnaire booklet at 2, 3 or 4 years (N = 9025).
[5] UK population, 1994 GHS data.
[6] Age weighted 1994 GHS data for mothers.
[7] Age-weighted 1996 GHS data for women not in full-time education.
[8] Age-weighted 1996 GHS data for men not in full-time education.
[9] 1994-96 GHS data for married couples with children aged 0-4.
[10] 1994-96 GHS data for mothers of children aged 0-4.

5.3 Questionnaire booklets

5.3.1 'Background' booklet

The initial 'Welcome to TEDS' questionnaire contained questions about the twins and their families and included subsections asking about: personal and contact details of family members; the twins' feeding, sleeping and care arrangements; the adults in the home, their relationship to each other and to the twins, their age, education, and employment; the mother's prenatal experiences, details on the pregnancy and the twins' perinatal health; plus questions on twin similarity to establish zygosity.

5.3.2 2-year, 3-year, and 4-year booklets

Subsequent phases of data collection involved the mailing of questionnaire packs shortly before the twin's 2nd, 3rd and 4th birthdays, consisting of one parent

booklet and two test booklets, one for each twin. The parent booklets included questions asking about changes in family composition and circumstances, aspects of the home environment, and the twins' general health.

Details on the developmental assessments and the health related measures used in the analyses of this dissertation are given below.

5.4 Developmental assessments

5.4.1 Non-verbal cognitive ability (PARCA).

Non-verbal cognitive ability was assessed using age-appropriate versions of the Parent Report of Children's Abilities (PARCA: (Oliver, Dale, & Saudino, 2002; Saudino et al., 1998) The PARCA is an hour-long test developed from various standard measures of cognitive ability (e.g., McCarthy Scales of Children's Abilities: (McCarthy, 1972); Bayley Scales of Infant Development: (Bayley, 1993), as well as novel items designed specifically for the PARCA. It consists of several subtests within two sections: a parent-administered part in which the parent administers a battery of standard cognitive tasks to their children (e.g. design copying, item matching, block building and imitative action), and a parent-reported part, in which parents report on their twins' cognitive abilities (e.g., "Does your child recognise himself/herself when looking in a mirror?"). Because the PARCA was designed to assess non-verbal abilities, an effort was made to ensure that the items did not assess language-related skills. Details of the test material have recently been described (Price, Petrill, Dale, Eley, & Plomin, 2003).

Validation studies at 2 and 3 years have demonstrated good internal consistencies for both the parent-administered and the parent-reported subscales (Saudino et al., 1998; Oliver et al., 2002). The present analyses are based on a composite total score derived from the parent-administered and parent-reported sections of the PARCA at each age (Price et al., 2003).

5.4.2 Verbal Ability (MCDI).

Verbal performance was assessed using age-appropriate vocabulary and grammar scales from the MacArthur Communicative Development Inventory: UK Short Form (MCDI:UKSF; Fenson et al., 2000). This measure is an abbreviated and anglicised adaptation of the MacArthur Communicative Development Inventory (MCDI), a widely-used measure of early language development (Dale, Reznick, & Thal, 1998). The MCDI has been shown to have excellent internal consistency and test-retest reliability, as well as concurrent validity with tester-administered measures (Fenson et al., 2000). The MCDI:UKSF has similarly been found to offer a valid and cost-effective measure of early linguistic development, that additionally is suitable for use with UK samples.

Vocabulary production is assessed in the MCDI:UKSF by means of a 100 item-checklist asking parents to report on their children's production of root words (e.g. dog, game, gentle). A composite score is calculated by summing the number of words ticked. The vocabulary measure given at 2 years consisted of a list of 100 words that predicts the 680-word original version of the MCDI with very high accuracy ($r = 0.98$) (Fenson et al., 1994). The 3-year measure was a similar 100 item-checklist, taken from an upward extension of the MCDI. The 4-year measure was similarly constructed, and consisted of 48 items. Test-retest reliability data are not yet available for these 3- and 4-year extensions of the MCDI.

Grammar is assessed in the MCDI:UKSF by asking parents about their children's sentence complexity. The grammar scales at 2 and 3 years each comprise 13 questions. The first question asks whether the child is able to combine words, the remaining 12 items each present two sentences carrying the same meaning, with the first representing a developmentally simpler form (e.g. "why he run away?" vs. "why did he run away?"). Parents indicate the sentence in each pair that resembles most what their child is able to say. The 12 sentences are

different on the 2- and 3-year scales and are chosen to be representative of a norming sample for 2 and 3-year-olds. At age 4, parents were asked to describe the complexity of their child's speech using a global rating one of six categories from "not yet talking" through to "talking in long and complicated sentences". At each age the instrument also includes a developmentally appropriate set of questions about language comprehension, and aspects of semantic development (e.g. "does your child give reasons for things, using the word 'because'?"). Scoring details are provided by (Price et al., 2003).

5.4.3 Behaviour Problems (RRPSPC).

Behaviour problems were assessed at 2, 3 and 4 years using the Revised Rutter Parent Scale for Preschool Children (RRPSPC) (Hogg, Rutter, & Richman, 1997). The RRPSPC is based upon the Preschool Behaviour Questionnaire (Behar & Stringfield, 1974) which was itself a downward extension to the pre-school range of the original Rutter Parent Scale (Rutter, 1966). In addition to a total behaviour problem score, the RRPSPC provides scores on three aspects of behavioural difficulty--emotional, conduct and hyperactivity/inattention. The test-retest reliability of the original Preschool Behaviour Questionnaire was 0.87 (Rutter, Tizard, & Whitmore, 1970). At 4 years the wording was slightly adjusted for certain items to correspond to the equivalent items from the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) so that both scales could be constructed. The SDQ is currently used for data collection at age 7 as it has the advantage that it can be completed by both the twins' parents and their teachers.

Test scores were invalidated and excluded from the analyses if the scales described above were completed more than 6 months after the twins' birthday.

5.5 Health related measures

5.5.1 Asthma

Parent report data on asthma was available at ages 3 and 4 years. In the 3-year booklet parents were asked: "Does your child have problems with asthma or wheezing?". The 4-year booklet included the following question on asthma status: 'Have either of your twins been prescribed medicine to control asthma?' .

Both items were scored as binary ("Yes/No") responses for each twin.

5.5.2 Eczema

Details relating to the twins' skin problems and eczema were obtained at 3 and 4 years of age.

In the 3-year booklet parents indicated whether their twins had any problems with their skin (such as rash, spots or eczema) ("Yes/No"). The 4-year booklet contained five items relating to eczema. Initially, parents were asked whether either of their twins has ever had skin problems associated with itching and scratching (for example eczema) ("Yes/No"). If this question was answered with 'yes', four questions relating to further details on the skin condition were asked. It was asked whether the twins received any treatment (e.g. medicine, ointments) for their skin condition ("Yes/No"), where on the body the skin problem occurred (i.e. face, knees, elbows, wrist, ankles or other), the age at which the skin problem started and whether it was still present ("Yes/No").

5.5.3 Otitis Media

Parents reported on their twins' hearing on three occasions: in the family background, the 3-year and the 4-year booklet. Each of the booklets included questions relating to respiratory infections and chronic airway blockage both of which are frequent symptoms of otitis media.

The family background questionnaire contained 7 items and the 3-year and 4-year booklets both included a list of 6 items on otitis media. Details on individual items are appended (see Appendix 3).

Principal component analyses were applied to all available data at each point of assessment, resulting in a single principal component accounting for 31%, 35% and 37% of the variance at ages 1.5, 3 and 4 years respectively. All items loaded above 0.46 on this principal component, reflecting high interrelation between individual items and indicating the appropriateness to use a total score.

5.5.4 Weight and overweight

In the 3-year and 4-year booklets parents were asked to report the current body weight and height for themselves and for their twins. Weight was corrected for height using standardised residuals from the regression of height on weight. Although twin analyses conducted using body mass index (BMI) yielded similar results, weight corrected for height assures that weight is independent of height for our genetic analyses of weight (BMI correlates -0.16 with height in our sample at age 3 years and – 0.21 at age 4 years). Weight corrected for height is hereafter referred to as weight. Weight refers to the entire distribution including overweight children in the top 10% of the distribution.

5.5.5 Parent attitudes towards eating (PATE)

In addition to child's weight, parents were also asked about their attitudes towards their children's diet. Both the 3- and 4- year booklets included a list of 7 questions relating to the twins' eating patterns. Details on individual items are provided in Appendix 3. Principal component analyses were applied to the available data at each age of assessment. The analysis resulted in a single factor which explained 31% of the variance at both ages. All items loaded above .40 on this principal component and a total score was created.

The table below (Table 5.2) gives an overview of the measures that are subject of the present dissertation by age of assessment.

Table 5.2 Overview of developmental and health related measures by age of assessment

Measures	**Age of assessment**			
	1.5 years 'first contact'	2 years	3 years	4 years
Developmental assessments:				
Verbal ability (MCDI)		●	●	●
Non-verbal cognitive ability (PARCA)		●	●	●
Behaviour problems (RRPSPC)		●	●	●
Health related measures:				
Asthma			●	●
Skin problems / eczema			●	●
Otitis media	●		●	●
Height and weight			●	●
Parent attitudes towards eating (PATE)			●	●

5.6 Statistical analyses

The variables from the TEDS questionnaire booklets used in the analyses of this dissertation were investigated using the general statistics package SPSS (SPSS Inc., 2000). Univariate and multivariate quantitative genetic analyses based on maximum-likelihood model fitting techniques were carried out using the structural equation modelling program Mx (Neale, Boker, Xie, & Maes, 1999).

6 Asthma

6.1 Overview:

Although the genetic and environmental factors of asthma have been investigated later in life, few studies have focused on the early development of asthma.

The current study uses parent reports on their children's asthma status at ages 3 and 4 years. At both ages, prevalence rates for asthma are consistently greater for boys than girls across all zygosity groups and especially for boys and girls in DZos twin pairs. Twin probandwise concordances were significantly greater for MZ twins than DZss twins and DZos twins. Genetic influence is substantial whereas shared environmental influences were modest and not statistically significant.Asthmatic children had significantly higher means on the behaviour problems total score than non-asthmatic children, as well as on the subscales for anxiety and hyperactivity ($p<.001$). There were no significant differences for other areas of development such as cognition or language.

There were only weak relationships between asthma, hyperactivity, anxiety, conduct as well as behaviour problem total score. This indicates that it is unlikely that there are genetic or environmental links between childhood asthma and behavioural problems.

6.2 Introduction

Asthma is one of the most widespread health problems within industrialised societies and incidence rates have risen considerably over the last few decades (Beasley, Crane, Lai, & Pearce, 2000; ISAAC, 1998; von Mutius, 2000a). Prevalence rates for childhood asthma vary widely throughout the world, with the

highest rates (17%-30%) reported in the UK, Australia and New Zealand (ISAAC, 1998). Although the onset of asthma can occur at any age the usual time of disease onset is by school age (Larsen, 2001). Most cases of childhood asthma tend to become less severe over time and as many as half who developed asthma as children become asymptomatic by the time they reach adulthood (Cluss & Fireman, 1985).

It is reasonable to expect that environmental exposures to allergens are of primary importance for the occurrence and the development of asthma. Such environmental exposures should be shared by children living within the same family and thus should contribute to sibling similarity in the occurrence of asthma. Such shared environmental exposures include parental smoking, air pollution, domestic animals, dust mites as well as number of siblings and factors associated with socioeconomic status (von Mutius, 2000a; von Mutius, 2000b). The role of environmental exposures to allergens and their contribution to asthma has recently been reviewed (Helms & Christie, 1999; Becker, 2001). The relationship between asthma versus parental smoking and air pollution remains controversial (Tariq, Hakim, Matthews, & Arshad, 2000; von Mutius et al., 1994).

Results from twin studies have consistently found evidence that genetic factors contribute importantly to asthma. Correlations for monozygotic twins are consistently higher than for dizygotic twins suggesting the involvement of genetic factors (Laitinen, Rasanen, Kaprio, Koskenvuo, & Laitinen, 1998; Sarafino & Goldfedder, 1995; Edfors-Lubs, 1971; Hopper, Hannah, Macaskill, & Mathews, 1990; Nieminen, Kaprio, & Koskenvuo, 1991). Estimates of heritability range from 0.36 (Nieminen et al., 1991) to 0.87 (Laitinen et al., 1998; Skadhauge, Christensen, Kyvik, & Sigsgaard, 1999; Lichtenstein et al., 1997; Duffy, Martin, Battistutta, Hopper, & Mathews, 1990; Harris, Magnus, Samuelsen, & Tambs, 1997). Moreover, despite the reasonableness of shared environmental hypotheses about the origins of asthma, these twin studies consistently find little evidence for

shared environmental influence. However, most of the twin samples used in these studies involve a wide age range, typically from adolescence to adulthood, although one study (Lichtenstein et al., 1997) focuses on middle childhood (ages 7 to 9 years).

In addition to the genetic and environmental contributions to the condition *per se*, there is also some indication that childhood asthma affects early psychological development. For instance, there is evidence for a link between asthma and psychological adjustment in that several studies have found that asthmatic children are more likely to experience behavioural difficulties than healthy childen (Klinnert et al., 2000; Mrazek, Schuman, & Klinnert, 1998b), especially in relation to disease severity (Bussing, Halfon, Benjamin, & Wells, 1995; Butz et al., 1995; McQuaid et al., 2001). In a recent meta-analysis, the findings of 26 studies on the relationship between asthma in nearly 5000 children and adolescents and their behavioural adjustment were reviewed and it was concluded that children with asthma experienced more behavioural difficulties than healthy children (McQuaid et al., 2001).

In contrast, however, studies investigating the links with other developmental domains, such as cognition, found no significant differences between asthmatic and non-asthmatic children on school performance and academic achievement (Rietveld & Colland, 1999; Annett, Aylward, Lapidus, Bender, & DuHamel, 2000). It is also possible that such problems arise not specifically because of atopy, but rather due to the medications used to treat these conditions. There has been some evidence for the adverse effects of some medical treatments on cognitive performance, particularly in relation to hay fever (Blaiss, 2000). In contrast, for asthma there is only weak evidence and if any effects are found they are often only minimal or transitory (Lindgren et al., 1992; Bender, Ikle, DuHamel, & Tinkelman, 1998).

So far, no previous twin study has focussed on asthma in preschoolers and examined its relationship to development. The Twins' Early Development Study (TEDS) provides an opportunity to test in early childhood the hypotheses that heritability for asthma is substantial and shared environmental influences are modest using a large representative sample of twins. Furthermore the sample facilitates an investigation into the potential existence of developmental differences and correlates between asthmatic and non-asthmatic children. It is hypothesised that asthmatic children score significantly higher on measures of behaviour problems but that there are no differences for verbal and non-verbal cognitive domains between asthmatic and non-asthmatic twins. In addition, it is expected that a significant correlation will be found between asthma and behaviour problems allowing a follow-up investigation implementing multivariate genetic analyses.

6.3 Sample:

The TEDS sample has been described previously in some detail (see Chapter 5). The analyses and results described in this chapter are based on all families who provided information on the twins' asthma status at ages 3 and 4 years.

Zygosity was ascertained by a parent questionnaire on twins' physical similarity which was found to be highly accurate (Price et al., 2000); see Chapter 5 for more details).

Twins' asthma status was ascertained at ages 3 and 4 years. In the 3-year-booklet parents were asked: "Does your child have problems with asthma or wheezing?", and the 4-year-booklet included the following question about asthma: "Have either of your twins been prescribed any medication to control asthma?".

Only twins with complete information on zygosity and asthma status at each age were included in the analyses. At 3 years, the sample consisted of a total

of 5773 twin pairs (1965 MZ, 1922 DZss and 1886 DZos) and at 4 years details were available for 7121 twin pairs (2407 MZ, 2398 DZss, 2316 DZos).

For bivariate analyses, the samples at both ages were based on all twins with valid data on the developmental assessments on language (MCDI), cognition (PARCA) and behaviour problems (RRPSPC).

6.4 Statistical Methods:

Twin similarity for asthma was assessed using probandwise concordance rates. As mentioned earlier, probandwise concordance rates are calculated as twice the ratio of the number of concordant pairs divided by twice the number of concordant pairs plus the number of discordant pairs. Furthermore, tetrachoric correlations were also calculated from pairwise contingency tables. Tetrachoric correlations were used as an index of twin similarity towards disease liability and for genetic model-fitting analyses. Tetrachoric correlations are based on the assumption of an underlying continuous distribution of liability to asthma despite the dichotomous measurement of asthma.

Twin concordances and correlations were interpreted on the basis of classic twin theory in respect to how the contribution of genes and environment can account for similarity and differences in relation to the different levels of genetic relatedness between MZ and DZ twin pairs (see Chapter 3 for details).

The tetrachoric correlations were used in structural equation modelling procedures (MX; Neale, 1997) in order to estimate genetic and environmental components of variance.

6.5 Results:

6.5.1 Univariate analyses:

Table 6.1 summarises sample sizes, prevalence, probandwise concordance rates, and tetrachoric correlations by zygosity and gender groups at

ages 3 and 4 years. The prevalence rates for asthma are somewhat higher for MZ than DZ twins and also greater in males as opposed to females. In addition, for all twins concordances and tetrachoric correlations are substantially greater for MZ twins than for DZ twins, implicating genetic influence. Shared environmental influences appear to be modest because the MZ correlations only moderately exceed heritability estimated by doubling the difference between the MZ and DZ correlations. Correlations for opposite-sex DZ twins are lower than correlations for same-sex DZ twins but not significantly so, warranting more research on possible gender differences in genetic and environmental influences.

Table 6.1: Sample sizes, prevalence, concordances, and tetrachoric correlations for asthma in twins at ages 3 and 4 years

Age 3 years								
Group	Pairs (N)	Probands (N)	Prevalence of Asthma (%)	Discordant Pairs (N)	Concordant Pairs (N)	Probandwise Concordance Rate (%)	Tetrachoric Correlations	95% Confidence Interval
Male MZ	911	267	14.7	89	89	50	0.85	0.79-0.90
Female MZ	1054	277	13.1	107	85	60	0.82	0.76-0.88
All MZ	*1965*	*544*	*13.8*	*196*	*174*	*47*	*0.84*	*0.80-0.88*
Male same sex DZ	985	336	17.1	210	63	24	0.44	0.33-0.54
Female same sex DZ	937	272	14.5	178	47	21	0.45	0.32-0.57
All same sex DZ	1922	608	15.8	388	110	22	0.45	0.36- 0.52
Male opposite sex DZ		350	18.6					
Female opposite sex DZ		245	13.0					
All opposite sex DZ	1886	595	15.8	425	85	16	0.30	0.21-0.39
All DZ	*3808*	*1203*	*15.8*	*813*	*195*	*19*	0.37	0.31-0.43
Total	***5773***		***15.1***	***1009***	***369***	***27***		

(Table 6.1 continued)

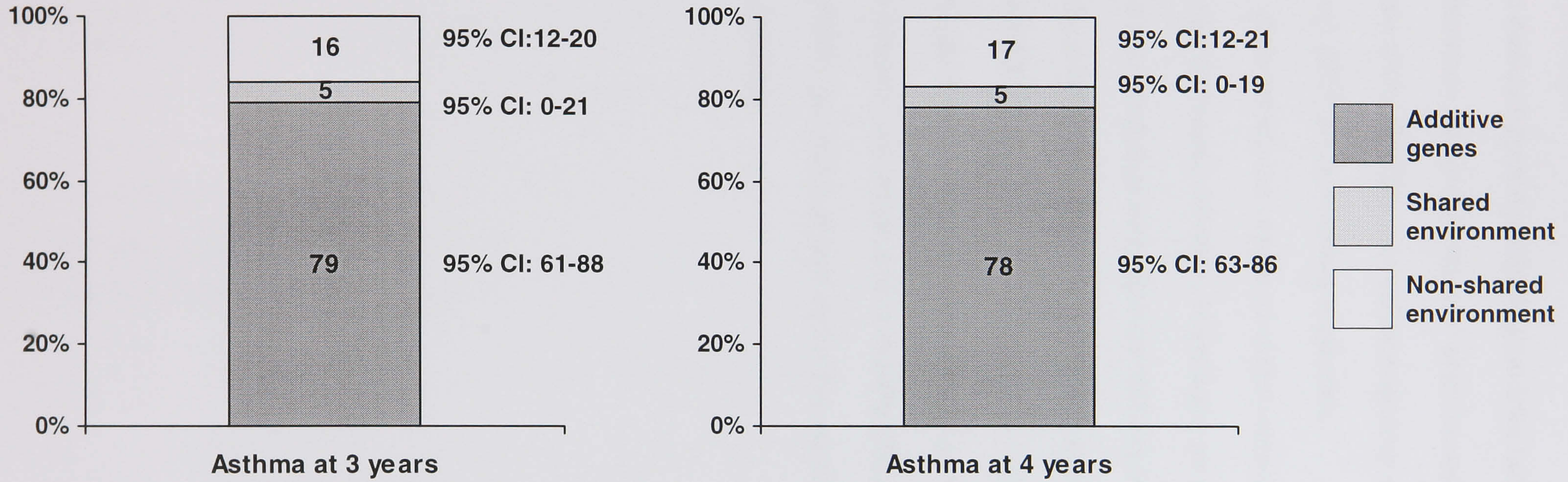
Age 4 years								
Group	Pairs (N)	Probands (N)	Prevalence of Asthma (%)	Discordant Pairs (N)	Concordant Pairs (N)	Probandwise Concordance Rate (%)	Tetrachoric Correlations	95% Confidence Interval
Male MZ	1117	469	21.0	159	310	66	0.81	0.75-0.85
Female MZ	1290	436	16.9	142	294	67	0.86	0.81-0.89
All MZ	*2407*	*905*	*18.8*	*301*	*604*	*67*	*0.83*	*0.80-0.86*
Male same sex DZ	1198	490	20.5	274	216	44	0.50	0.40-0.58
Female same sex DZ	1200	404	16.8	272	132	33	0.37	0.26-0.47
All same sex DZ	2398	894	18.6	546	348	39	0.44	0.37- 0.51
Male opposite sex DZ		490	21.2					
Female opposite sex DZ		334	14.4					
All opposite sex DZ	2316	824	17.8	560	264	45	0.33	0.25-0.40
All DZ	*4714*	*1718*	*18.2*	*1106*	*612*	*36*	0.39	0.34-0.44
Total	***7121***	***2623***	***18.4***	***1407***	***1216***	***46***		

Maximum-likelihood liability model-fitting estimates of genetic and environmental influences on asthma at ages 3 and 4 years are shown in Fig 6.1 and are based on same-sexed twins only.

At age 3 years the liability model of common effects – with estimates between males and females set to be equal – fit the data well ($\chi^2_{(8)}$= 11.50, p=0.18). Genetic influence is substantial (a^2=.79; 95% CI: .61-.88). Shared environmental influence is small and non-significant (c^2=.05; CI: .00-.21). Non-shared environmental influence was modest and significant (e^2=.16; CI: .12-.20). A comparison between males and females reduced the fit of the model and implied that differences in estimates between genders were insignificant.

At age 4 years the common effects model also provided a good fit to the data ($\chi^2_{(8)}$= 8.26, p=0.31). However, the subsequent comparison between males and females indicated somewhat higher heritability in girls (a^2=.84, CI: .81-.88) as opposed to boys (a^2=.61, CI: .41-.82), although this difference is not statistically significant.

Figure 6.1 Maximum likelihood liability model estimates of genetic and environmental effects on asthma at ages 3 and 4 years



6.5.2 Bivariate Analyses:

In order to evaluate potential aetiological links between asthma and development, differences between asthmatic and non-asthmatic children were assessed for verbal ability (MCDI), non-verbal cognitive ability (PARCA) and for behaviour problems (RRPSPC) including subscales.

Table 6.2 summarises the results of mean comparisons between the group of asthmatic and non-asthmatic children. There were no significant differences between the groups for language development (MCDI) or cognition (PARCA). However, asthmatic children scored significantly higher than non-asthmatic children on the RRPSPC total score, as well as on all of the subscales at age 3 years ($p<.001$). At age 4 years, there were no differences for the MCDI or the mean differences between asthmatic and non-asthmatic children remained significant for RRPSPC ($p<.001$), as well as for the subscales on anxiety ($p<.05$) and hyperactivity ($p<.001$).

Table 6.2 Standardised mean scores for behaviour problems (RRPSPC), language (MCDI) and non-verbal cognitive development (PARCA) and results of analysis of variance (ANOVA) between asthmatic and non-asthmatic children assessed at ages 3 and 4 years.

Age 3 years	Non Asthmatic N=7733		Asthmatic N=1357		ANOVA	
	Mean	SD	Mean	SD	F	p
Behaviour Problems (RRPSPC)	-0.03	0.99	0.19	1.05	54.65	.000
– subscale anxiety	-0.03	0.99	0.14	1.04	37.69	.000
– subscale conduct problems	-0.02	0.99	0.12	1.05	24.08	.000
– subscale hyperactivity	-0.02	1.00	0.09	1.01	13.69	.000
Language ability (MCDI)	0.00	0.99	0.00	1.03	0.00	.992
Non-verbal cognitive ability (PARCA)	-0.01	1.00	0.04	1.01	2.16	.142

Age 4 years	Non Asthmatic N=9548		Asthmatic N=2122		ANOVA	
	Mean	SD	Mean	SD	F	p
Behaviour Problems (RRPSPC)	-0.02	0.99	0.09	1.04	16.43	.000
– subscale anxiety	-0.01	0.99	0.06	1.02	8.76	.003
– subscale conduct problems	0.00	0.99	0.03	1.02	2.43	.119
– subscale hyperactivity	-0.02	0.99	0.08	1.03	15.31	.000
Language ability (MCDI)	0.00	1.00	0.00	1.00	0.01	.926
Non-verbal cognitive ability (PARCA)	0.00	1.00	0.00	1.01	0.01	.931

In contrast to the Pearson correlation coefficient (used to assess relationships between continuous variables), point-biserial correlations (r_{pb}) estimate the degree of association between a dichotomous and a continuous scale. In order to evaluate the link between asthma and development, point biserial correlations between asthma and all developmental measures were calculated and are shown in Table 6.3. The results show that no relationships are significant and that there are only weak links between asthma, hyperactivity (r = .04), anxiety (r = .04) as well behaviour problem total score (r = .05). This finding suggests that it is unlikely that common aetiological factors (environmental or genetic) exist for childhood asthma and behaviour problems.

Table 6.3 Point biserial correlations for asthma, language development, non-verbal cognitive development and behaviour problems at ages 3 and 4 years

	Asthma	
Point biserial correlations	**3 years N=9090**	**4 years N=11670**
Behaviour Problems (RRPSPC)	0.05	0.02
– anxiety	0.05	0.02
– conduct problems	0.05	0.00
– hyperactivity	0.02	0.02
Language (MCDI)	0.03	0.02
Non-verbal (PARCA)	0.01	0.02

6.6 Conclusion

The present findings indicate that asthma is highly heritable in preschool children exposed to the same environmental allergens in the home. Shared environmental factors such as rearing environment, family diet and air pollutants seem to play a minor role. The present results are in line with but also extend those of studies of older twins that have found little or no shared environmental

influence (Laitinen et al., 1998; Harris et al., 1997). Nonetheless, genotype-environment interaction (GxE) remains a possibility in the sense that some individuals might be more susceptible genetically to shared environmental exposures in the home.

A limitation of the study is that asthma status relied on parental reports of medical treatment for asthma because this was deemed the most valid single item that could be asked of parents in relation to their children's asthma. The candidate is not aware of any studies that have explicitly assessed the validity of parental reports of asthma. However, there is some evidence which suggests that parent reports on a variety of childhood illnesses (including asthma) are reliable when compared to paediatricians' records (Pless & Pless, 1995). The study included 288 families with children aged between 1-13 years. Parents completed a questionnaire on their child's medical history over the last year. For parent reported asthma 91% of cases were in agreement with their children's medical records. In addition, the study found greater accuracy for mothers' responses as opposed to fathers', and parents of younger children showed better recall. Nonetheless, it would be useful in future research to include other respiratory symptoms such as the occurrence of wheezing over the last twelve months. Because wheezing is quite common in young children, with incidences as high as 50% (Martinez et al., 1995; Brooke et al., 1995; Wright, 2002) it is possible that the assessment of medical treatment for asthma in TEDS includes transient respiratory problems. It would also be useful to assess children's history of respiratory illness because individuals who contract viral infections during infancy or early childhood are more likely to develop asthma (Papadopoulos & Johnston, 2001; Gern & Busse, 2002; Osur, 2002). It is possible that these early infections increase vulnerability to respiratory illnesses later on as well as increasing sensitivity to potential environmental triggers.

The results of mean differences between asthma status and development showed that at both assessment ages children with asthma had somewhat higher scores for behaviour problems than their non-asthmatic peers, but there were no differences for language and non-verbal cognitive development.

Bivariate analyses found no significant association between asthma and behaviour problems implying that aetiological factors for asthma and behaviour problems in preschoolers are likely to be independent of each other.

To date, there is only one study which has investigated the shared aetiology between allergic disorders and behaviour problems (Wamboldt, Schmitz, & Mrazek, 1998). The findings suggested a shared genetic link between general atopy and behaviour problems, particularly internalising problems. The study used a sample of school aged twins (mean age 7.5 years). Data collection was based on parent reports and the questionnaires included a continuous scale to assess general atopy status. Although the majority of questions that were asked related to general allergy, the atopy scale also included two items on asthma. Hence, there is some suggestion that a relationship between asthma and behaviour problems may exist. It is possible that associations with behaviour problems may be dependent on the severity of general atopy or that such links may start to emerge at a later age. However, whether and how these findings relate to asthma *per se* is presently unknown. Although the present results did not find a link between asthma and behaviour problems, future studies are needed to explore and replicate any associations between specific atopic disorders and behaviour problems.

The genetic contribution to asthma is likely to be polygenic with many distinct genes contributing to susceptibility. Genome screening studies have found markers on most chromosomes that appear to be associated with asthma related phenotypic factors (Blumenthal & Blumenthal, 2002; Castro, Telleria, & Blanco-Quiros, 2001; Haagerup et al., 2002). A way forward in research is to bring genetic

and nonshared environmental strategies together to study the developmental interplay between nature and nurture.

6.7 Acknowledgements

An early analysis of part of this data has been published, for which I thank the co-authors:

Koeppen-Schomerus, G., Stevenson, J., & Plomin, R. (2001). Genes and environment in asthma: a study of 4 year old twins. Archives of Disease in Childhood, 85, 398-400.

7 Eczema

7.1 Overview

Atopic dermatitis or eczema is a common multifactorial disease which has increased substantially in frequency. Although the genetic and environmental factors of eczema have been investigated later in life, few studies have focused on the early development of eczema in preschoolers. The purpose of the present study was to expand on the results of previous twin studies on eczema and to quantify the genetic and environmental contributions towards the condition as well as to explore any potential developmental associations using a population twin sample aged 3 and 4 years.

As mentioned in Chapter 5, the assessments were based on parent reports on their children's eczema status as well as on aspects of their development. At both ages, prevalence rates for eczema were similar for boys and girls across zygosity groups indicating no differences between genders. Twin probandwise concordances were significantly greater for MZ twins than DZ twins. In addition, tetrachoric correlations were more than twice as large for MZ as opposed to DZ twins indicating that additive as well as non-additive genetic factors may contribute to expression of eczema.

Univariate results at both ages suggest that the effects of additive and non-additive genetic influence on eczema are substantial and that the effects of shared environment are not statistically significant.

Children with eczema scored significantly higher on the behaviour problems total score than unaffected children, as well as on all of the subscales at both ages. There were no significant differences between the groups for other areas of development such as cognition or language.

Multivariate results showed that there were only weak associations between eczema and behaviour problems as well as subscales which imply that the factors that influence eczema and behaviour problems are aetiologically distinct.

7.2 Introduction

Atopic eczema is a chronic skin condition affecting between 5% and 20% of children at one time or other (Fennessy, Coupland, Popay, & Naysmith, 2000). Similar to other atopic disorders such as asthma and hay fever, the prevalence of eczema has increased significantly over the second half of the last century, for reasons largely unknown. It has been well established that there is a genetic component to eczema as indicated by several twin and family studies (Sarafino, 2000; Bradley et al., 2000; Lichtenstein et al., 1997; Mikkilinenil et al., 2001; Schultz Larsen et al., 1986).

Yet despite its genetic component, evidence from various sources also suggests that environmental factors are involved in the expression of the disease. The rapid increase in prevalence and the social and geographical variation in disease expression cannot be due to genetic factors but imply a strong role for changing environmental exposures and lifestyle factors for eczema.

As outlined previously in Chapter 2, numerous studies have found evidence that environmental factors may cause sensitisation and development of allergic symptoms and disease in susceptible individuals (von Mutius, 2000b; McNally et al., 2001; Nicolai & von Mutius, 1997; Schultz Larsen et al., 1986). It is well documented that increased exposure to selected allergens (e.g., air pollution, climate changes, house dust mites and smoking) are important risk factors for the development of eczema and allergic sensitization. However, it is unclear when and how long an environmental exposure needs to be present until the disease becomes established in genetically predisposed individuals. Furthermore, it is still

unknown which specific environmental factors are involved in causing the increase in prevalence of eczema and allergic disease.

Due to the early age of onset of the condition it is likely that various lifestyle and environmental influences operating prenatally or in early infancy may be crucial in the aetiology of eczema. Early life seems particularly important, when the initiation of allergic disease may result from the genetic and environmental modification of the immune interaction between mother and child. The identification of environmental factors offers an opportunity for prevention of the disease, and unraveling the genetics of atopic conditions is likely to have important advances for eczema diagnosis and treatment.

In addition to causing considerable physical discomfort and compromised quality of life (Kiebert et al., 2002), skin conditions such as dermatitis, psoriasis and eczema have been found to increase the risk for developmental and psychological difficulties (Lapidus & Kerr, 2001). Although most of the literature involves adult samples (White, Horne, & Varigos, 1990; Buske-Kirschbaum, Geiben, & Hellhammer, 2001; Gieler, Ehlers, Hohler, & Burkard, 1990), there is also evidence that eczema can have implications for the psychosocial adjustment of children (Lapidus et al., 2001; Absolon et al., 1997). For instance, children with eczema have been found to show increased levels of anxiety and greater dependency on their parents as opposed to children who are not affected by the condition (Daud et al., 1993). At school age, affected children might also be more frequently absent from school since the itching and physical discomfort that accompany eczema can often lead to disordered sleeping patterns which can have an effect on children's learning ability and performance (Dahl, Bernhisel-Broadbent, Scanlon-Holdford, Sampson, & Lupo, 1995; Bender, 1999). In addition, in some studies eczema has also been found to be associated with a poor self-image and self-confidence (Lapidus et al., 2001). A recent review on the relationship between atopic disorders and learning in childhood further suggests

that children with atopic conditions may experience learning problems as well as adaptation problems at school, but the review also argues that the extent of these problems has been overrated and that differences seem to be small (Bender, 1999).

Although there is ample evidence for psychosocial differences between eczema sufferers and unaffected individuals, there are hardly any studies as to why these differences exist and how they emerge. The candidate is currently aware of only one twin study which explored the relationship between atopic symptoms and behaviour problems in childhood (Wamboldt et al., 1998). The study used a community sample of over 200 twin pairs (aged 4-11 years) and found the cross correlation between atopic symptoms and internalising behaviours to be moderate (r= .21). Subsequent bivariate genetic analyses indicated that this association was mainly mediated by shared genetic influences which explained 77% of the covariance. This study provides some evidence for a shared genetic risk between atopy and some types of behaviour problems.

TEDS provides an ideal opportunity to study the early origins of eczema within a large representative sample of preschool twins. In line with the findings from other twin studies, it is hypothesised that genetic influence on eczema at ages 3 and 4 years is substantial and that the effects of shared environment will be modest.

An additional focus of this chapter is to assess potential developmental differences between children affected by eczema and unaffected children and to explore the mediation of any significant relationships between development and eczema status. The domains under investigation are language and non-verbal cognitive ability as well as behaviour problems. It is expected that children with eczema show higher rates of behaviour problems than controls, especially in relation to the domain of anxiety. In addition, it is expected that behaviour problems and eczema status are correlated and that this relationship is mediated

by shared genetic factors. No significant differences between the two groups are expected regarding language development and cognition.

7.3 Methods

7.3.1 Sample

The TEDS sample has been described in some detail in Chapter 5. The analyses and results described for the current study are based on all families who provided details on the twins' skin problems and eczema status at ages 3 and 4 years. As described previously, twin zygosity was ascertained by parent ratings of physical similarity (see Chapter 5 and Price et al., 2000).

Table 7.1 compares the sociodemographic characteristics between twins affected and unaffected by eczema based on paternal occupational status. Contrary to some reports, within the present sample there was no indication that eczema was more prevalent within the higher social classes (I and II).

All twins with complete information on zygosity and the items on eczema at both ages were included in the analyses. The sample consisted of a total of 3133 twin pairs (1114 MZ, 1012 DZss and 1007 DZos).

Table 7.1 Sociodemographic characteristics of families with twins affected and unaffected by eczema defined by paternal occupational status

		Eczema			
		unaffected		***affected***	
	Father's occupation:	*3 years*	*4 years*	*3 years*	*4 years*
		4582 children in 2291 families	4588 children in 2294 families	1684 children in 842 families	1678 children in 839 families
I	Professional	12.0%	11.7%	11.2%	11.7%
II	Managerial, technical	30.9%	31.3%	32.7%	31.5%
IIIN	Skilled – non-manual	8.4%	8.7%	8.4%	7.6%
IIIM	Skilled – manual	24.0%	23.9%	22.3%	22.4%
IV	Partly skilled manual	6.7%	6.5%	6.0%	6.5%
V	Unskilled manual	2.7%	2.7%	3.3%	3.2%
	Missing cases	15.5%	15.1%	16.2%	17.0%

7.3.2 Measures:

The 3-year-booklet contained one question on skin problems and eczema: “Does your child have skin problems (rash, spots or eczema)?” In the 4-year booklet parents were asked whereas the 4-year-booklet included the following two questions: "Have either of your twins ever had skin problems associated with itching or scratching (for example eczema)?" Parents indicated whether their twins had skin problems at the moment, if they had been affected previously or whether they were unaffected. Families with twins with current or previous skin conditions were then asked whether the twins had taken any treatments (such as medicine or ointments) over the past 12 months for these conditions.

All twins with ‘Yes’ responses to the skin problem item at age 3 years were selected as probands. At age 4 years, probands were selected if their parents had indicated (a) the occurrence of past or present skin conditions (i.e. either ‘yes, previously’ or ‘yes, at present’) in addition to (b) having undergone medical treatment over the last 12 months.

For bivariate analyses, the sample consisted of all twin pairs with valid data on developmental assessments of language (MCDI) and cognitive ability (PARCA) as well as of behaviour problems (RRPSPC) at ages 3 years (N_{total}=2509) and at 4 years (N_{total}=5835).

7.3.3 Statistical methods:

As in the previously reported analyses on asthma (see Chapter 6), twin similarity for eczema was assessed by calculating probandwise concordance rates and tetrachoric correlations derived from pairwise contingency tables. A comparison of concordances and correlations between MZ and DZ twin pairs provided an initial index of the contributions of genetic and environmental factors towards the phenotype ‘eczema’. As described in earlier sections, greater similarity of MZ twins as opposed to DZ twins implies genetic influence.

Structural equation models were applied to the data to estimate genetic and environmental effects using the software package MX (Neale, 1997). As described earlier in Chapter 3, possible causes of variation are additive genes (A), dominance (D), shared environment (C) and non-shared environment (E). With data on MZ and DZ twins reared together, the significance of additive genetic variance, specific environmental factors, and either a common environmental or a dominance parameter can be tested.

For the purpose of the present analyses, alternative models were tested for eczema at both ages. Starting from the ACE-model, and assuming additive genetic (A), shared environmental (C), and non-shared environmental (E) factors, the shared environmental factor was replaced by one accounting for variance owing to dominance (d^2), the ADE-model. Since the effects of shared environmental factors and genetic dominance are confounded in studies of twins reared together, a full model including additive and dominance genetic factors and specific and shared environmental factors (ACED) cannot be tested. Finally, the AE model tested the significance of the shared or common environmental factors (c^2).

7.4 Results

7.4.1 Univariate analyses:

Table 7.2 presents sample sizes, prevalences, probandwise concordance rates, and tetrachoric correlations for MZ and DZ twins combined as well as for male and female MZ and DZ and opposite-sex twins separately at ages 3 and 4 years. There were no significant differences in correlations or concordances for eczema between males and females. Furthermore, eczema prevalence was similar across zygosity and gender groups.

For eczema at both ages, MZ correlations exceeded those of DZ twins, implicating genetic effects. In addition, the DZ correlations were less than half the

MZ correlation, possibly indicating the existence of non-additive genetic or dominance effects.

In Table 7.3 ACE, ADE and AE models are shown with their corresponding fit statistics. In addition, the percentages of explained variance by each of the parameters included in the respective model are shown. The three models were tested and the difference in goodness of fit was compared by the chi-squared goodness-of-fit statistics at each age. Akaike's Information Criterion (AIC) and likelihood ratio tests were used to indicate the most parsimonious and best fitting model.

Although the fit indices for both ACE and ADE models were good, the ADE model fitted the data better at age 3 years ($\Delta \chi^2 = 6.94$) and at age 4 years ($\Delta \chi^2 = 3.41$). As expected from the similarity of correlations between boys and girls, no sex differences in genetic or environmental variance contributions towards eczema were found at any age and the ADE-model with equal parameters for males and females remained the best fitting model. In addition, shared environmental influences were non-significant since no change in chi-square was observed when the AE model was tested.

Table 7.2: Sample sizes, incidences, concordances, and tetrachoric correlations for eczema at ages 3 and 4 years

Group	Pairs (N)	Probands (N)		Prevalence of Eczema (%)		Discordant Pairs (N)		Concordant Pairs (N)		Probandwise Concordance Rate (%)		Tetrachoric Correlations (95% CI)	
		3 years	4 years	3 years	4 years	3 years	4 years	3 years	4 years	3 years	4 years	3 years	4 years
MZm	509	274	267	26.9	26.2	86	61	188	206	68	77	.80 (.71-.86)	.90 (.84-.94)
MZf	605	317	338	26.2	27.9	111	88	206	250	65	74	.76 (.67-83)	.85 (.79-.90)
All MZ	*1114*	*591*	*605*	*26.5*	*27.1*	*197*	*149*	*394*	*456*	*66*	*75*	*.78 (.72-.83)*	*.87 (.83-.91)*
DZm	512	301	273	29.4	26.7	185	159	116	114	39	42	.22 (.07-.36)	.35 (.20-.48)
DZf	500	262	277	26.2	27.7	162	159	100	118	38	43	.28 (.13-.42)	.34 (.20-.48)
All DZss	*1012*	*563*	*550*	*27.8*	*27.2*	*347*	*318*	*216*	*232*	*38*	*42*	*.25 (.14-.35)*	*.34 (.24-.44)*
DZos-m	--	283	268	28.1	25.3	--	--	--	--	--	--	--	--
DZos-f	--	247	255	24.5	26.6	--	--	--	--	--	--	--	--
All DZos	*1007*	*530*	*523*	26.3	*26.0*	346	311	184	212	35	40	.20 (.09-.31)	.33 (.23-.43)
All DZ	*2019*	*1093*	*1073*	*27.1*	*26.6*	*693*	*629*	400	444	37	41	.22 (.15-.30)	.34 (.27-.41)
Total	***3133***	***1684***	***1678***	***26.9***	***26.8***	***890***	***778***	***794***	***900***	***47***	***53***	**--**	**--**

Table 7.3. Model fitting results for twin data on eczema, goodness-of-fit statistics and percentages of explained variance of the model parameters.

Model	χ^2	df	p	AIC	a^2	c^2	d^2	e^2
3 years								
ACE	12.73	8	.122	-3.27	.76 (.67-.81)	.00 (.00-.07)	---	.24 (.19-.30)
ADE	5.79	8	.671	-10.21	.22 (.00-.62)	---	.56 (.14-.82)	.22 (.17-.28)
AE	12.73	9	.175	-5.27	.76 (.70-.81)	---	---	.24 (.19-.30)
4 years								
ACE	7.13	8	.522	-8.87	.87 (.78-.90)	.00 (.00-.08)	---	.13 (.10-.17)
ADE	3.72	8	.881	-12.28	.50 (.09-.88)	---	.37 (.00-.79)	.13 (.09-.17)
AE	7.13	9	.623	-10.87	.87 (.83-.90)	---	---	.13 (.10-.17)

Note:
ACE = additive genetic effect, shared and non-shared environment;
ADE = additive genetic, nonadditve/dominance genetic, and non-shared environmental effects;
AE= additive genetic effect and non-shared environment;
df = degrees of freedom; p = probability; AIC= Akaike's Information Criterion
a^2 = proportion of variance explained by additive genetic factors
c^2 = proportion of variance explained by shared environment factors
d^2 = proportion of variance explained by non-additive genetic effects or dominance
e^2 = proportion of variance explained by non-shared environment factors

Hence, all of the models show substantial genetic influence and no shared environment. At age 3 years the results of the ADE model suggest moderate effects due to additive (a^2=.22; 95% CI: .00-.62) and non-additive genetic influences (d^2=.56; 95% CI: .14-.82). Non-shared environmental influence is modest and significant (e^2=.22; CI: .17-.28). Similarly, at age 4 years additive genetic influences are modest (a^2=.50; 95% CI: .09-.88) and although the model indicates the presence of non-additive genes, d^2 is not statistically significant (d^2=.37; 95% CI: .00-.79). The remaining variance is again explained by non-shared environmental factors (e^2=.13; 95% CI: .09-.17).

7.4.2 Bivariate Analyses:

In order to investigate aetiological links between eczema and development, children with and without eczema were assessed for verbal ability (MCDI), non-verbal cognitive ability (PARCA) and for behaviour problems (RRPSPC) including subscales.

Table 7.4 summarises the results of mean comparisons between the group of twins affected by eczema and unaffected children. There were no significant mean differences between the groups for language (MCDI) or cognitive ability (PARCA). However, children with eczema had significantly higher scores than unaffected children on the behaviour problem total score, as well as on all of the subscales at age 3 years ($p<.001$). At age 4 years, children with eczema scored significantly higher on the RRPSPC total scale ($p<.001$), as well as on the subscales for conduct problems ($p<.001$). Mean group differences remained marginally significant for subscales on hyperactivity and on anxiety ($p<.05$). As at age three, no significant differences between the groups were found for verbal and non-verbal cognitive development.

Table 7.4: Standardised mean scores for behaviour problems (RRPSPC) including subscales, language (MCDI) and non-verbal cognitive development (PARCA) and results of analysis of variance (ANOVA) between children affected and unaffected by eczema at ages 3 and 4 years.

Age 3 years	***Eczema***					
	unaffected N=3661		***affected N=1357***		***ANOVA***	
	Mean	***SD***	***Mean***	***SD***	***F***	***p***
Behaviour Problems (RRPSPC)	-0.06	0.98	0.15	1.04	42.32	.000
– subscale anxiety	-0.03	0.98	0.08	1.04	13.06	.000
– subscale conduct problems	-0.05	0.98	0.13	1.03	29.34	.000
– subscale hyperactivity	-0.04	1.00	0.11	1.00	21.10	.000
Language ability (MCDI)	0.00	1.00	0.00	1.00	0.02	.877
Non-verbal cognitive ability (PARCA)	0.00	0.99	-0.01	1.01	0.10	.757

Age 4 years	***Eczema***					
	unaffected N=3797		***affected N=1375***		***ANOVA***	
	Mean	***SD***	***Mean***	***SD***	***F***	***p***
Behaviour Problems (RRPSPC)	-0.03	0.99	0.08	1.03	12.52	.000
– subscale anxiety	-0.03	0.98	0.07	1.04	9.28	.002
– subscale conduct problems	-0.03	1.00	0.07	1.00	10.17	.001
– subscale hyperactivity	-0.02	0.99	0.05	1.03	3.85	.050
Language ability (MCDI)	-0.02	1.01	0.04	0.98	3.52	.061
Non-verbal cognitive ability (PARCA)	-0.02	0.99	0.05	1.02	5.88	.015

Although the mean differences for behaviour problems are significant, given the relatively large sample size, it should be noted that the effect sizes are small, about .1 to .2 of a standard deviation difference. The effect sizes are highlighted in Table 7.5 which presents point-biserial correlations. The results show that the relationships are all non-significant and that there are only weak links between eczema status, hyperactivity, anxiety and total behaviour problems score ranging from r=.00 to r=.07. This finding suggests that common aetiological factors are unlikely to explain the relationship between eczema and behaviour problems in children as young as 3 and 4 years. These relationships are too weak to permit multivariate genetic analyses.

Table 7.5 Point biserial correlations between eczema and developmental outcome measures at ages 3 and 4 years.

	Eczema	
	3 years *N=5018*	***4 years*** *N=11670*
	r_{pb}	r_{pb}
Behaviour Problems (RRPSPC)	0.07	0.03
– anxiety	0.07	0.03
– conduct problems	0.05	0.02
– hyperactivity	0.05	0.00
Language (MCDI)	0.02	0.01
Non-verbal (PARCA)	0.01	0.02

7.5 Conclusion

The findings of this study demonstrate important familial and unique environmental influences on the development of eczema in preschool-aged twins. The current results suggest that genetic influence on eczema is substantial explaining 76% of disease liability at age 3 and 87% at age 4 under the ACE model. If the dominance model (ADE) is selected, dominance explained between 37% and 56% of the variation in liability and additive genetic factors explained between 22% and 50%. The hypothesis that shared environmental factors play a

role in eczema in childhood was not supported. The acceptable fit of the AE model indicates that shared environmental effects on eczema are not significant. The remaining variation that was not explained by additive or non-additive genes was accounted for by non-shared environmental influences. Although there was an indication for the differential effects of additive and non-additive/dominance genes, it was not possible to discriminate between the effects of a^2 and d^2 due to a lack of power. The current results need to be replicated as due to the wide confidence intervals for estimates of additive and non-additive genes it was not possible to adequately quantify these differences.

The strong genetic component found for eczema as well as for asthma (see Chapter 6) indicates that both disorders are highly heritable and molecular genetic findings suggest that they are likely to be influenced by multiple genes. Because the remaining contributions towards disease risk for both conditions are almost entirely due to non-shared environment, the present findings further imply that common environmental risk factors are unlikely to play a role in disease expression. Therefore, environmental influences which have differential effects on different children within the same family seem to be more important. In other words, these factors operate on an individual basis rather than on a family basis, so, they affect each family member differently. Although non-shared environment is difficult to specify, it is possible that an environmental factor which is thought of as shared, is in fact non-shared since it has a unique effect on the individual. Children might differ in their individual susceptibility towards certain environmental events or triggers that are linked to disease expression and manifestation. These events could possibly include the types of food eaten, allergen exposure, infections, colds and illnesses.

A limitation of the current study is the lack of specificity of disease definition due to the small number of items included to assess eczema. Thus, some misclassification of disease status is likely to occur in this study. This probably

arose because of the tendency for parents to use the term 'eczema' to describe a number of associated skin conditions that are characterised by redness, dryness and itching. The prevalence in TEDS of almost 30% for eczema is comparatively high in relation to the national UK prevalence in school children of between 15-20% (Charman, 1999). Higher prevalence estimates for reported eczema than population prevalence estimates suggest that some over-reporting of eczema by parents was apparent in the sample.

There were no developmental associations between eczema status, language and cognitive ability. However, the findings suggest that children with eczema had higher scores for behaviour problems than unaffected children. As the bivariate correlation was only weak, bivariate genetic analysis of the relationship between eczema and behaviour problems could not be applied.

In the literature, links between atopic disorders and behaviour problems have been widely reported, especially in relation to the degree of disease severity (McGee, Stanton, & Sears, 1993; Roth, Beyreiss, Schlenzka, & Beyer, 1991; Absolon et al., 1997). It is possible that in the present analysis this association was not detected because of the way eczema status was assessed. Due to the dichotomous Yes/No coding it was not possible to compare children with severe eczema to those with milder forms of the condition. A relationship between eczema severity and increasing levels of behaviour problems has been reported previously (Absolon et al., 1997), here, as many as 60% of children with moderate and severe eczema showed behaviour problems.

In summary, the current results provide additional support for the hypothesis that that eczema is highly heritable in young children. Genetic factors explain the largest part in liability towards eczema whereas specific environmental factors account for the remaining variation. It is likely that the relationship between genetic predisposition and interacting environmental triggers is complex and it is

important to facilitate a better understanding between the disease and behaviours, home and lifestyles as well as the role of additional external environmental factors.

8 Weight and Overweight

8.1 Overview

Many twin, family and adoption studies document genetic influence on individual differences in weight. However, much less is known about genetic influences on overweight and about the genetic links between weight and overweight. Additionally, little is known about environmental influences contributing to overweight, such as family environment and child-specific aspects of environment. There is some evidence which suggests that parent feeding styles are linked to the development of overweight in children. Furthermore, there is support that being overweight or obese is associated with problems of psychological adjustment in adolescence and adulthood. However, few studies have reported on this relationship in early childhood.

The genetic and environmental contributions of weight and overweight in childhood were assessed at ages 3 and 4 years, and the relationship between parent feeding styles and children's weight was explored. Genetic factors contributed substantially both to individual differences in weight throughout the distribution and to the mean weight difference between overweight children and the rest of the population. Unlike results later in life, weight and overweight in childhood also suggest substantial shared family environmental influence. Results were similar for boys and girls.

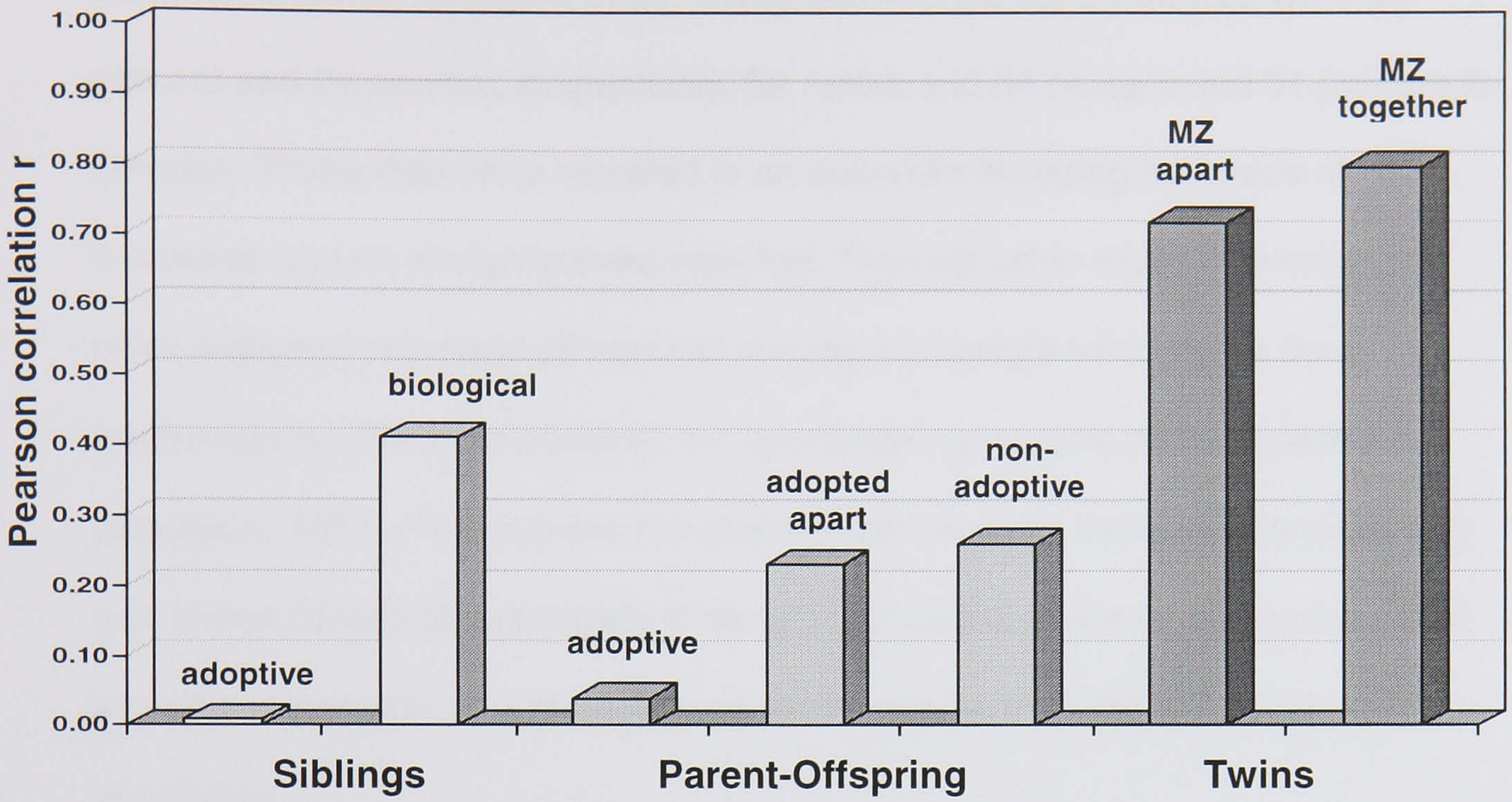
For parent feeding style measures correlations for MZ and DZ twins were high and virtually identical. Also, there were no mean or correlational differences on parental feeding style between overweight and normal weight children. These results suggest that parent feeding style contributes little to weight differences and overweight in preschool children.

The findings further showed that weight was not linked to any of the developmental assessments and that there were no mean differences between overweight and normal weight children for measures of language, non-verbal cognitive development or behaviour problems.

8.2 Introduction

It is often assumed in the media that individual differences in weight are attributable to factors such as eating habits, lack of exercise and self-control and that these factors are environmental in origin. However, twin and adoption studies in adulthood consistently lead to the conclusion that genetic factors account for the majority (about 70 %) of the variance of weight (Maes et al., 1997). The rest of the variance is environmental but despite the commonly held assumption that weight is caused by lifestyle habits that are learned early in life and therefore shared by children growing up in the same family, in fact such shared environmental influences appear to be of negligible importance in adulthood. The importance of shared environment on body weight can be observed by comparing the correlations between family members of differing degree of genetic relatedness (see Figure 8.1). For instance, a direct test of shared environmental influence is the correlation between genetically unrelated (i.e. adoptive) relatives: adoptive 'siblings' correlate .01 and adoptive parents and their adopted children correlate .00 on body weight (Grilo & Pogue-Geile, 1991). Equally, offspring appear to resemble their biological parents in weight to a similar degree, irrespective of whether they were adopted away or not. In addition, identical twins reared together, who share both 100% of their genes and their family environments, show no greater resemblance than identical twins reared apart, who share only their genes.

Figure 8.1 Similarity of body weight based on data from family, adoption and twin studies (based on the review by Grilo and Pogue-Geile, 1991)



However, with just two exceptions (Medlund, Cederlöf, Floderus-Myrhed, Friberg, & Sorensen, 1976; Stunkard, Foch, & Hrubec, 1986), previous genetic studies have investigated individual differences in weight throughout the distribution rather than overweight or obesity. This is an important distinction because genetic and environmental factors responsible for overweight can differ from genetic and environmental factors responsible for the normal range of variation (Plomin et al., 2001). There are at present only two twin studies, both involving adults, that analysed overweight twins (Medlund et al., 1976; Stunkard et al., 1986). Using the fifth percentile as a selection criterion in a US study of 4071 male twin pairs (Stunkard et al., 1986), twin similarity for MZ twins was substantially higher than for DZ twins. Although no formal model-fitting analyses were conducted, the pattern of twin resemblances suggests that results for overweight are similar to those consistently found in the literature for the normal variation in weight: substantial genetic influence (78-81%) and no shared environmental influence. Roughly similar results emerged from a Swedish study of

12,556 same-sex male and female twin pairs using the seventh percentile as a selection criterion (Medlund et al., 1976). MZ and DZ concordances were 45 percent and 24 percent, respectively, for males and 54 percent and 31 percent for females. These data were reported in an appendix including hundreds of measures and no analyses were reported. The only other study of overweight twins analysed individual differences among overweight twins rather than analysing the difference between the overweight group and the population (Børjeson, 1976). This approach is problematic because the question is not why one obese person differs slightly in weight from another obese person but rather why obese persons as a group are so much heavier than the rest of the population.

Additionally, even if the heritability of overweight and the heritability of weight are both substantial, this does not necessarily imply that the same genetic factors are responsible for overweight and weight. Understanding the genetic links between the normal and abnormal is a key issue for research on the origins of obesity in general and especially for molecular genetic attempts to identify specific genes responsible for heritability. That is, to what extent does overweight or obesity represent the quantitative extreme of the same genetic and environmental factors responsible for normal variation in weight? DF extremes analysis (described earlier in Chapter 3 DeFries et al., 1985) broaches this issue by assessing relatives of selected probands on a quantitative measure rather than merely assessing concordance for a qualitative diagnosis. Until now, no previous study implemented DF extremes analysis to address the extent to which normal variation in weight is linked genetically to overweight or obesity. The hypothesis that overweight represents the quantitative extreme of the same genetic and environmental factors responsible for normal variation in weight follows from quantitative trait locus (QTL) theory (Plomin, Owen, & McGuffin, 1994). QTL theory suggests that genetic influence on common complex traits such as weight is likely

to be due to multiple genes of varying effect size. If multiple genes are involved, weight is likely to be distributed quantitatively as a dimension and overweight is likely to be the extreme of the same distribution rather than representing an aetiologically distinct disorder.

Nevertheless, in addition to the substantial influence of genetic factors on body weight, environmental factors are also of importance. As mentioned earlier, environmental effects on body weight have been found to be non-shared rather than shared (Grilo et al., 1991; Maes et al., 1997). Therefore, nonshared environments may be an additional target to explore factors involved in the aetiology of weight and overweight. It is reasonable to assume that especially during childhood, environmental factors contribute importantly to the development of eating habits and food preferences later on (de Castro, 1993; de Castro, 1999). Although several studies have assessed the genetic links between parent and child weight (Danielzik, Langnase, Mast, Spethmann, & Muller, 2002; Safer, Agras, Bryson, & Hammer, 2001), relatively little is known about the extent to which parents (especially overweight parents) select environments that promote overweight in their children. Family eating patterns as well as the types of foods and their availability in the home are all part of the environments of children's early experiences. The family environment also comprises parents' own eating behaviours and their child-feeding practices. A number of studies on the behavioural mediators of familial patterns of overweight have suggested a link between parents' own eating behaviours, their parenting practices and their children's eating behaviours (Koivisto, Fellenius, & Sjoden, 1994; Klesges et al., 1983; Hill, 2002; Saelens, Ernst, & Epstein, 2000; Spruijt-Metz, Lindquist, Birch, Fisher, & Goran, 2002).

Family environment research has also attempted to assess the potential aetiological role of specific parental characteristics (other than their own weight) on

the development of weight and obesity in their children. In particular, parents who are overweight, who have problems controlling their own food intake, or who are concerned about their children's risk for overweight may adopt particular child-feeding practices in an attempt to prevent overweight in their children. However, research on the relationship between specific parental feeding styles – such as encouragement and control – and children's obesity risk have produced inconclusive findings. Some studies report a positive relationship between children's weight and parental encouragement to eat (Klesges et al., 1983; Klesges, Stein, Eck, Isbell, & Klesges, 1991) whereas others found no such relationship (Koivisto et al., 1994; Drucker, Hammer, Agras, & Bryson, 1999). Equally, studies comparing the degree of parental feeding control in overweight and normal weight children have also been unable to find conclusive evidence (Saelens et al., 2000; Robinson, Kieran, Matheson, & Haydel, 2001; Hill, 2002). These inconclusive findings may further corroborate behavioural genetic studies which have found little effect of shared environment on the variation of body weight.

Parental encouragement for physical activity has been observed to be positively correlated with children's activity levels and negatively correlated with children's weight (Klesges, Malott, Boschee, & Weber, 1986). Such findings may of course be mediated genetically as well as environmentally. Furthermore, the direction of any environmental influence in such studies remains ambiguous and it is unlikely that cross-sectional studies on the association between parental feeding practices and children's weight will succeed in partitioning causes from effects. Although parental feeding behaviours may be causally related to their child being overweight, it is possible that the parent acts in response to the child's weight. For example, a parent might be more controlling over what the child eats either out of concern that the child may become overweight or in response to a child who already is overweight. However, although eating and feeding behaviours are

largely shaped by environmental factors, there is evidence that individual differences in these behaviours also have a genetic basis (de Castro, 1993; de Castro, 1999).

Another area of research is concerned with the psychological health of overweight and obese individuals. The physical appearance of overweight and obese people can lead to social discrimination and stigmatisation with potentially adverse psychological consequences for the individual. Several studies on adults and adolescents suggest that obese individuals experience higher rates of psychological problems (e.g. depression, low self-esteem) as opposed to normal weight individuals (Roberts, Strawbridge, Deleger, & Kaplan, 2002; Falkner et al., 2001; Kielmann & Herpertz, 2003). However, very few studies exist on the psychological associations of overweight and obesity in young children. One study investigated the relationship between weight status and self-concept and found that overweight children as young as five years experience lower levels of self-esteem as well as of perceived physical and cognitive ability (Davison & Birch, 2001). However, this study was based on a relatively small sample which included only girls.

Understanding the shared biological and social determinants which link psychological problems to obesity may broaden the current knowledge of the causal pathways involved and inform the prevention and treatment of both disorders.

In the present chapter the following hypotheses will be tested. Firstly, that in early childhood, overweight is as heritable as weight and that weight and overweight are linked genetically. Secondly, that part of the variation in parental feeding styles is genetically mediated and that there are differences in parent feeding practices in relation to body weight. Thirdly, that there are no developmental links or differences between overweight children and normal weight

children for verbal and non-verbal cognitive ability as well as for behaviour problems.

8.3 Methods

8.3.1 Sample

The TEDS sample used for the present analyses has been described in some detail in Chapter 5. The initial target sample for this study consisted of 9025 families who completed the 'background' booklet and at least one other booklet. Measures of height and weight as well as on parent feeding styles were collected when the twins were 3 and 4 years old. A total of 2456 families provided complete details on twins' weight at both ages, and for 2308 families additional details on parent feeding practices were available.

Therefore, the sample used for the univariate analyses of weight and overweight included 4912 children in 2456 twin pairs: 804 identical (monozygotic, MZ) pairs, 836 same-sex non-identical (dizygotic, DZss) pairs, with approximately equal numbers of boys and girls, and 816 opposite-sex DZ pairs (DZos). For the purpose of DF analyses only same-sex twins were included. Overweight twins were selected as falling at or above the 90th percentile for the distribution of weight at each assessment age. At age 3 years there were 250 MZ twin probands and 248 DZss twin probands in 156 MZ twin pairs and 174 DZss twin pairs, and at age 4 years there were 278 MZ probands and 230 DZss probands in 164 MZ twin pairs and 162 DZss twin pairs.

For multivariate analyses on the relationship between parent feeding practices and child weight a total of 2308 families provided valid data and the sample included 754 MZ, 790 DZ same sex, and 764 DZ opposite sex twin pairs.

8.3.2 Measures

Weight and Overweight

As described previously, parents of twins reported on their children's weight and height near the twins' third and fourth birthdays. Weight was corrected for height using standardised residuals from the regression of height on weight. Although twin analyses conducted using body mass index (BMI) yielded similar results, weight corrected for height assures that weight is independent of height for the genetic analyses of weight (BMI correlates -0.14 and -0.17 with height at ages 3 and 4 years respectively). Weight corrected for height is hereafter referred to as weight. Weight refers to the entire distribution including overweight children in the top 10% of the distribution. Overweight children were selected as falling at and above the 90th percentile of weight.

Parent feeding style

Details on parent feeding style were available at ages 3 and 4 years. At each age parents were asked a set of 7 questions relating to their attitudes towards feeding their twins. In over 97% of cases the questionnaires were completed by the twins' mothers. Details on individual items and how the total scale was derived have been previously provided (see Chapter 5 and Appendix 3).

Developmental assessments

Developmental measures used in TEDS were described in some detail in Chapter 5. The assessments used for the present analyses included language (MCDI), non-verbal cognitive ability (PARCA), and behaviour problems (RRPSPC) at ages 3 and 4 years.

Zygosity

Zygosity information was obtained from a parent-report questionnaire which has proved to be 95% reliable in this sample when compared to zygosities as

assigned by DNA markers (see Chapter 5 for further details and Price et al., 2000 for full information on zygosity determination in TEDS).

Demographic characteristics

Information on parental educational level and occupation was obtained from the family 'background' booklet.

Fathers' occupations were classified according to the Registrar General's Classification of Occupations from Class I (professional) to class V (unskilled manual) (OPCS, 1991). Mothers were grouped according to their level of education, to represent the proportion of mothers without any formal qualifications, having achieved the minimum UK educational qualifications (no formal qualifications, CSEs, GCSEs or O-levels), those who completed further education (i.e. A-levels, diploma) and those with higher education qualifications (i.e. university degrees).

8.3.3 Univariate Analyses

Details on behavioural genetic analyses and the twin method have been described in some detail in Chapter 3.

To reiterate briefly, the essence of the twin method is the comparison of the phenotypic resemblance between monozygotic (MZ) twins, who are genetically identical because they derive from the same fertilised egg, and dizygotic (DZ) twins, who are 50 per cent similar genetically because they derive from two separately fertilised eggs. The twin method implicates genetic influence to the extent that MZ twins are more similar for a trait than are DZ twins. Heritability, a statistic that indexes the size of the genetic effect, refers to the proportion of phenotypic (observed) variance that can be attributed to genetic variation. Doubling the difference between the correlations for MZ and DZ twins provides a rough approximation to heritability, because MZ twins are twice as similar

genetically as DZ twins (Falconer, 1960). However, the error in such estimates may be large. Nevertheless, this initial method provides a rough estimation of the expected proportions of genetic and environmental factors on the phenotypic variance.

Individual Differences in Weight

In practice, structural equation model-fitting analyses of variance/covariance matrices rather than simple comparisons of twin correlations are used to estimate genetic and environmental parameters and to provide confidence intervals for these estimates (Neale et al., 1992). The ACE model (as described in Chapter 3, see Fig. 3.1) estimates parameters for additive genetic variance (A), common or shared environment (C), and environmental influences that are not shared (E). The model assumes that genetic effects are additive and that MZ and DZ twins experience equally similar environments.

Differences between Weight and Overweight

Children in the top 10% of the distribution of weight were selected as being 'overweight' and were compared to the rest of the sample at ages 3 and 4 years. This design makes it possible to apply DF extremes analysis (DeFries et al., 1985; DeFries et al., 1988) in order to assess the extent to which genetic and environmental factors that affect the extreme of the distribution also affect a measured quantitative trait that indexes normal variation throughout the distribution. For twin pairs in which at least one member of the pair was in the tenth pecentile in weight, probandwise concordances were computed for MZ and DZ twins. However, twin concordances only provide a rough index of genetic and environmental influence on overweight defined as a dichotomous disorder. Rather than assigning a dichotomous diagnosis (i.e., overweight or not) to the twin partners (co-twins) of the probands and assessing concordance, DF extremes

analysis (DeFries et al., 1988) addresses the aetiology of the links between the normal and abnormal by incorporating quantitative trait scores of the co-twins of probands. The essence of DF extremes analysis is that if the mean weight difference between the probands and the population is due to genetic factors, co-twins of MZ probands will be heavier than co-twins of DZ probands. This difference is used to estimate 'group heritability' which is different from the usual heritability estimate which refers to differences between individuals rather than to mean differences between groups. DF extremes analysis can yield evidence for genetic influence only to the extent that the quantitative trait is genetically linked to the disorder, that is, to the extent that the same genes affect the disorder and the dimension. However, showing group heritability for a quantitative trait measure and showing that group heritability is similar to the usual individual differences heritability does not unequivocally prove that the same genes are responsible for the disorder and the dimension. For example, a rare mutation with a major effect might be over-represented in the extreme group but account for little variation in the normal range.

For DF extremes analysis, weights corrected for height were standardised and transformed to adjust for group mean differences between MZ and DZ groups. The basic DF model allows predicting the co-twin's score from the proband's score. Because the proband mean is transformed to a mean of 1.0 and the unselected population to a mean of 0.0, doubling the difference of the co-twin's mean scores between MZ and DZ twins estimates their 'group heritability'. 'Group shared environment' – twin resemblance not explained by genetic factors – can be estimated by subtracting group heritability from the MZ group familiality.

DF analyses were conducted using a double-entered dataset so that both members of a twin pair could be selected as probands.

8.4 Results

8.4.1 Preliminary Analyses

Table 8.1 compares the overweight and normal weight groups for uncorrected weight, for mother's self-reported weight, BMI, age, and education, and for father's occupation. The weight of the children in the top 10 per cent of the distribution is about 1.8 SD (= mean SD; range: 1.2 –3.9) above the population mean at both ages. Mother's weight of the overweight children is between 0.3 – 0.4 SD above the population mean. There are no statistically significant differences between the two groups for maternal age, maternal education or paternal occupation ($p<.01$).

Table 8.1: Weight and demographic characteristics of normal-weight and overweight twins at ages 3 and 4 years

		Normal Weight ***(< 90th percentile)***		***Overweight*** ***(>=90th percentile)***	
		3 years	*4 years*	*3 years*	*4 years*
		N=4421 twins in 2199 families	N=4416 twins in 2193 families	N=491 twins in 257 families	N=496 twins in 263 families
Mean	Twin weight (kg)	14.0	16.1	17.6	20.2
	Twin weight[1]	-0.24	-0.24	1.81	1.81
	Twin BMI (kg/m^2)	15.6	15.3	19.3	19.2
	Maternal weight (kg)	65.0	65.4	68.7	70.5
	Maternal BMI (kg/m^2)	24.0	23.4	25.0	25.3
	Maternal age (years)	31.6	32.5	30.7	31.8
Maternal education:					
	Without formal qualification	4.6%	4.3%	4.8%	7.0%
	Completed mandatory education[2]	51.8%	52.1%	55.5%	53.6%
	Completed further education[3]	21.4%	21.1%	18.8%	21.1%
	University degree	22.2%	22.5%	20.9%	18.3%
Father's occupation:					
I	Professional	14.0%	14.3%	15.5%	12.5%
II	Managerial, technical	34.9%	34.8%	29.3%	30.2%
IIIN	Skilled – non-manual	8.1%	8.3%	9.4%	8.5%
IIIM	Skilled – manual	23.0%	23.2%	25.9%	24.0%
IV	Partly skilled manual	5.3%	5.3%	6.3%	6.5%
V	Unskilled manual	2.4%	2.3%	1.8%	2.6%
	Missing cases	12.3%	11.8%	11.8%	15.7%

[1] weight corrected for height
[2] obtained UK secondary school qualifications 'GCSEs'
[3] obtained A-levels or 'Higher National Diploma/Certificate' (UK qualifications) or 'CSEs'

8.4.2 Individual Differences in Weight

For the total sample absolute within pair weight differences were calculated for uncorrected weight (kg) and are shown in Fig 8.2. The comparison of absolute weight differences shows that between zygosity groups, MZ twin pairs were more similar in their weight than DZ pairs suggesting genetic influence. In addition, twin correlations of weight corrected for height indicate substantial heritability and moderate shared environmental influence for both boys and girls. The intraclass twin correlations for weight are summarised in Table 8.2 according to zygosity and assessment age. All twin correlations are substantial in size, and statistically

significant. For both males and females, the twin correlations are greater for MZ than DZ pairs for weight at ages 3 and 4 years, suggesting the presence of genetic influences regardless of sex. The pattern of correlations also suggests some influence of shared environmental effects, since the same-sex DZ correlations all take values that exceed half the relevant MZ correlation. Sex differences in the twin correlations are small and indicate slightly greater genetic influence and slightly less shared environmental influence for boys than for girls. The twin correlations for opposite-sex pairs at age 3 are somewhat lower than those for same-sex DZ pairs, implying a possibility of sex-specific influences which could be either genetic or environmental. Furthermore, twin correlations for weight were highly similar to the correlations for BMI (see Table 8.2).

Figure 8.2 Absolute weight differences within twin pairs (kg) by zygosity at ages 3 and 4 years

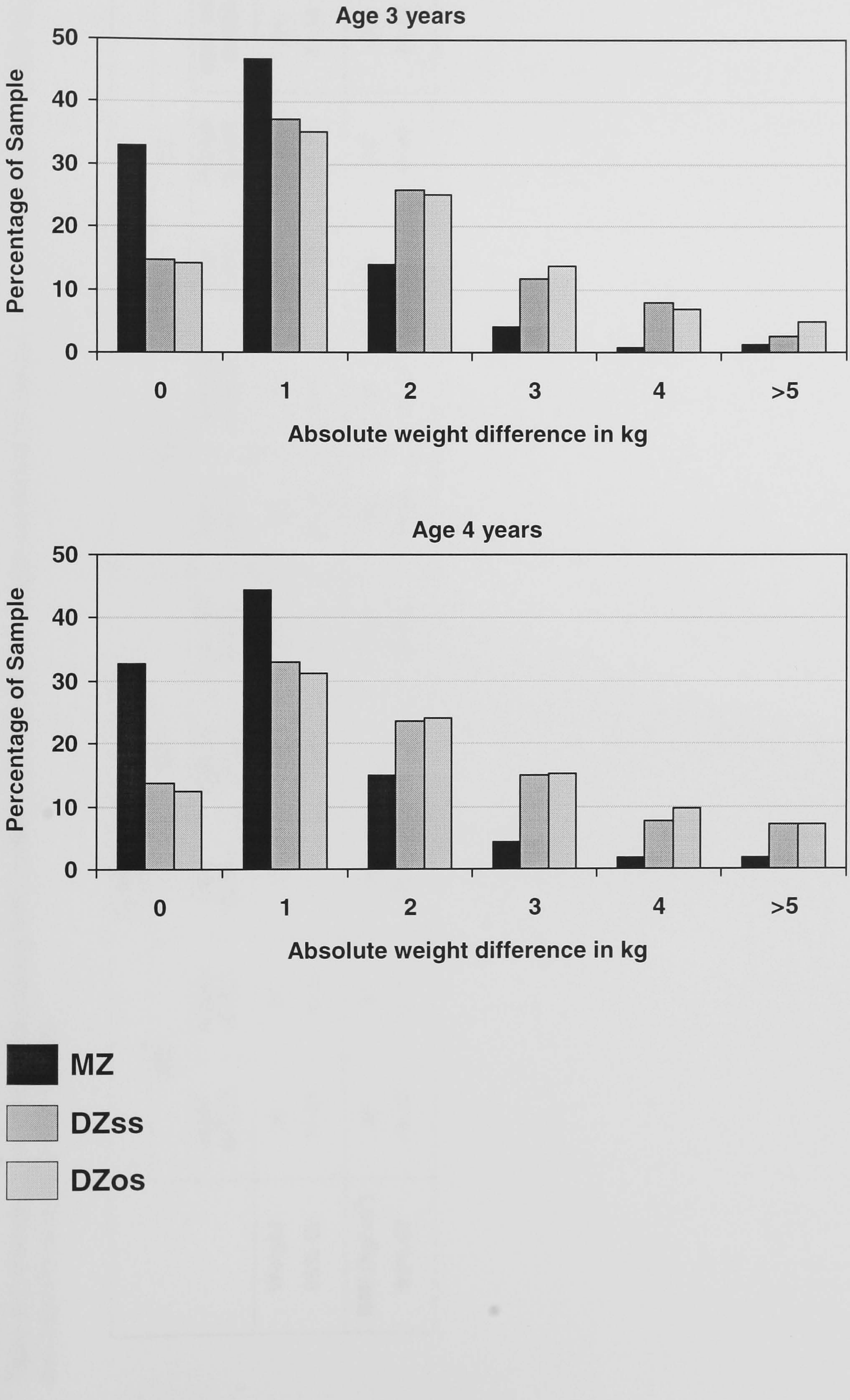


Table 8.2: Intraclass correlations (including 95% confidence intervals) for weight (corrected for height) and body mass index (BMI) by gender and zygosity at ages 3 and 4 years

	3 Years					4 years				
	MZ		DZ			MZ		DZ		
	male N=372	female N=432	male N=412	female N=424	opp. sex N=816	male N=372	female N=432	male N=412	female N=424	opp. sex N=816
Weight	.81	.80	.57	.64	.49	.85	.85	.60	.55	.54
95% CI	.79-.83	.78-.83	.53-.62	.60-.68	.46-.53	.83-.88	.84-.87	.56-.65	.50-.60	.51-.58
BMI (kg/ m^2)	.80	.81	.60	.67	.52	.86	.86	.63	.60	.59
95% CI	.78-.83	.79-.84	.56-.65	.64-.71	.49-.56	.84-.88	.85-.88	.59-.67	.56-.65	.56-.63

Results gleaned from these twin correlations were confirmed using maximum-likelihood model-fitting analyses of variance-covariance matrices using the statistical software package MX (Neale, 1997).

The ACE model can be used to estimate the same parameters across genders (common ACE model) as well as to derive different parameters for males and females separately (sex differences model). The goodness-of-fit statistics and parameter estimates are summarised in Table 8.3. The most parsimonious model was the common ACE model which fitted the data well at both ages (at age 3 years: $\chi^2 = 20.71$, *df* =12, *ns*; at age 4 years: $\chi^2 = 14.28$, *df* = 12, *ns*). At age 3 years there was some evidence for gender differences and heritability estimates were higher for boys (.58; 95% CI: .49 – .66) than for girls (.33; CI: .22 – .46) whereas estimates of shared environment were greater in girls (.46; 95% CI: .34 – .56) as compared to boys (.23; 95% CI: .16 – .32). At age 4 years the effect of gender differences was less pronounced and estimates of genetic factors were very similar for boys (.52; 95% CI: .40 –.67) and girls (.56; 95% CI: .44–.66); shared environmental estimates at 4 years were .34 (95% CI: .22–.45) and .26 (95% CI: .17–.38) for boys and girls respectively. The overlapping 95% confidence intervals for the parameter estimates for boys and girls outlined above also suggest that sex differences are weak and not statistically significant.

Table 8.3. Model fitting results on weight assessed at ages 3 and 4 years including goodness-of-fit statistics and percentages of explained variance of the model parameters.

Age 3years	χ^2	***df***	***p***	***RMSEA***	***AIC***	$\Delta\chi^2$	Δ ***df***	***p***	h^2		c^2		e^2	
									male	***female***	***male***	***female***	***male***	***female***
Sex differences	14.26	9	.113	.004	-3.74	--	--	--	.58 (.49-.66)	.33 (.22-.46)	.23 (.16-.32)	.46 (.34-.56)	.19 (.16-.22)	.21 (.18-.24)
Common ACE**	20.71	12	.055	.015	-3.29	6.45	3	ns	.48 (.41-.55)		.32 (.26-.39)		.20 (.18-.22)	

Age 4 years	χ^2	***df***	***p***	***RMSEA***	***AIC***	$\Delta\chi^2$	Δ ***df***	***p***	h^2		c^2		e^2	
									male	***female***	***male***	***female***	***male***	***female***
Sex differences	10.20	9	.335	.008	-7.80	--	--	--	.52 (.40-.64)	.56 (.44-.66)	.34 (.22-.45)	.26 (.17-.38)	.14 (.12-.17)	.17 (.15-.20)
Common ACE**	14.28	12	.283	.006	-9.72	4.96	3	ns	.54 (.47-.61)		.30 (.24-.36)		.16 (.14-.18)	

** denotes the most parsimonious model of best fit
df = degrees of freedom, p=probability, AIC = Akaike's Information Criterion
RMSEA = Root Mean Square Error of Approximation
h^2, c^2, e^2 = percentage of explained variance due to genetic component (h^2), shared environmental component (c^2) and specific environmental component (e^2)

8.4.3 Differences between Overweight and Normal Weight Children

Children were selected from the top 10% of the distribution of weight corrected for height at age 3 and 4 years. The probandwise concordance rates are summarised in Table 8.4 and were obtained separately at each age for MZ and DZ twins by doubling the number of concordant pairs and dividing it by twice the number of concordant pairs plus the number of discordant pairs. Twin probandwise concordances at 3 years were 60% for MZ twins and 42% for same-sex DZ twins. At age 4 the concordance rates were 70% and 58% for MZ and DZ twins respectively.

Although concordance rates provide a useful index of risk of being affected by a disorder, formal statistical analyses are required to estimate the contributions of genetic and environmental influences of the disorder.

Table 8.4: DF extremes analyses: Probandwise concordances, transformed co-twin means, group heritability, shared environment and non-shared environment estimates for same sex MZ and DZ twins for overweight (defined as >+90th percentile) at 3 years and 4 years.

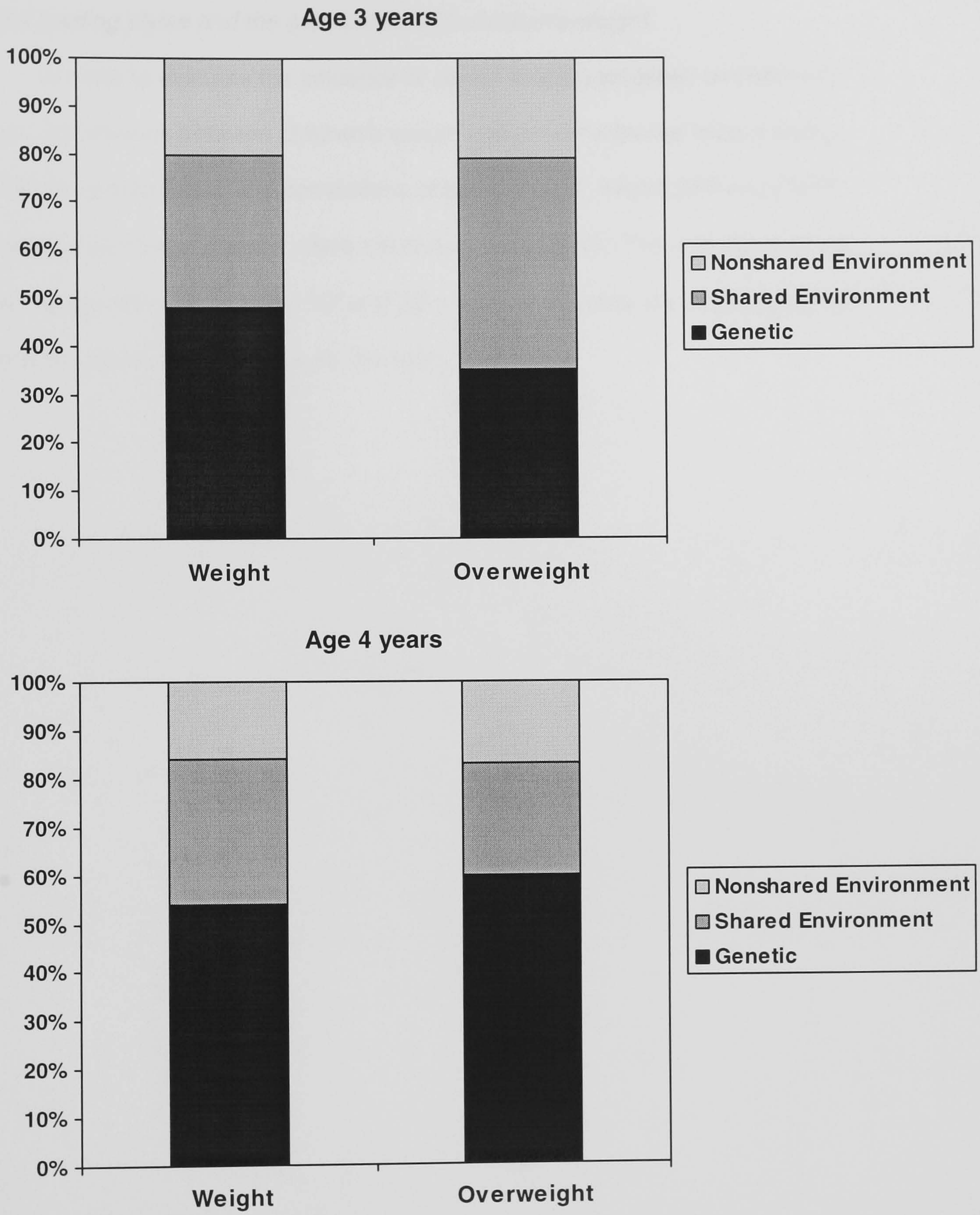
	Concordant pairs (N)	Discordant pairs (N)	Probandwise concordance rate	Transformed co-twin mean (SE)	h_2g	c_2g	e_2g
Age 3 years							
MZ	94	62	60%	.79 (± .04)	.35	.44	.21
DZss	74	100	42%	.61 (± .04)			
Age 4 years							
MZ	114	50	70%	.83 (± .03)	.60	.23	.17
DZss	68	94	58%	.53 (± .04)			

Notes: h_2g= group heritability estimate; c_2g=group shared environment estimate; e_2g=group non-shared environment estimate
Total N_{pairs} = 1640 (MZ=804 DZss=836)

DF extremes model-fitting analysis, which capitalises on the quantitative weight data for co-twins of overweight probands, yielded estimates of .35 (± .10) and .60 (± .10) for 'group heritability' at ages 3 and 4 years respectively. That is, as much as half of the average weight difference between the overweight probands and the population is due to genetic factors. This finding implies that genetic factors responsible for overweight overlap substantially with genetic factors responsible for normal variation in weight as assessed by the quantitative trait measure of weight corrected for height. The 'group' shared environment estimate is .44 (± .11) at age 3 years and .23 at age 4 years (± .12).

The following figure (Fig. 8.3) illustrates that heritability increases with age and that the estimates of genetic and environmental components of variance for weight and overweight are similar.

Figure 8.3 Genetic model-fitting results for weight and overweight (>=90th percentile for weight) at ages 3 and 4 years.



8.4.4 Multivariate analyses:

Parent feeding styles and the association with children's weight

In order to evaluate the influence of parent feeding practices on children's weight, correlations between children's weight and parent attitudes toward eating (PATE) were calculated. The correlations of twins' weight, height, BMI and PATE for the total sample at 3 and 4 years are shown in Table 8.5. The twin correlations show that correlations between MZ and DZ twins are equally high, suggesting that most of the variance is non-genetic in origin.

Table 8.5 Correlation matrix for MZ (N_{pairs}=754) and DZ twin pairs (N_{pairs}=1554) for weight, height, BMI and parent feeding attitudes (PATE) assessed at ages 3 and 4 years

		MZ Twins	Twin 1									
			3 years					4 years				
			Weight (kg)	Weight (corrected for height)	Height (m)	BMI (kg/m2)	PATE	Weight (kg)	Weight (corrected for height)	Height (m)	BMI (kg/m2)	PATE
Twin 2	3 years	Weight (kg)	0.81	0.68	0.47	0.58	-0.07	0.61	0.47	0.43	0.37	-0.05
		Weight (corrected for height)	0.68	0.80	0.03	0.78	-0.08	0.45	0.44	0.17	0.39	-0.06
		Height (m)	0.47	0.03	0.85	-0.14	0.00	0.45	0.20	0.55	0.09	0.00
		BMI (kg/m2)	0.58	0.78	-0.14	0.81	-0.09	0.36	0.39	0.06	0.37	-0.06
		PATE	-0.07	-0.08	0.00	-0.09	0.94	-0.05	-0.04	-0.03	-0.03	0.65
	4 years	Weight (kg)	0.61	0.45	0.45	0.36	-0.05	0.85	0.73	0.47	0.61	-0.03
		Weight (corrected for height)	0.47	0.44	0.20	0.39	-0.04	0.73	0.85	0.02	0.83	-0.02
		Height (m)	0.43	0.17	0.55	0.06	-0.03	0.47	0.02	0.90	-0.17	-0.04
		BMI (kg/m2)	0.37	0.39	0.09	0.37	-0.03	0.61	0.83	-0.17	0.86	0.00
		PATE	-0.05	-0.06	0.00	-0.06	0.65	-0.03	-0.02	-0.04	0.00	0.93

		DZ Twins	Twin 1									
			3 years					4 years				
			Weight (kg)	Weight (corrected for height)	Height (m)	BMI (kg/m2)	PATE	Weight (kg)	Weight (corrected for height)	Height (m)	BMI (kg/m2)	PATE
Twin 2	3 years	Weight (kg)	0.51	0.44	0.27	0.38	-0.02	0.33	0.24	0.25	0.18	-0.02
		Weight (corrected for height)	0.44	0.55	-0.03	0.55	-0.01	0.24	0.23	0.09	0.21	0.01
		Height (m)	0.27	-0.03	0.56	-0.15	-0.03	0.25	0.09	0.33	0.02	-0.05
		BMI (kg/m2)	0.38	0.55	-0.15	0.58	0.00	0.18	0.21	0.03	0.20	0.02
		PATE	-0.02	-0.01	-0.03	0.00	0.89	-0.02	-0.01	-0.03	-0.01	0.65
	4 years	Weight (kg)	0.33	0.24	0.25	0.18	-0.02	0.50	0.43	0.27	0.37	-0.04
		Weight (corrected for height)	0.24	0.23	0.09	0.21	-0.01	0.43	0.55	-0.04	0.56	-0.02
		Height (m)	0.25	0.09	0.33	0.03	-0.03	0.27	-0.04	0.58	-0.17	-0.03
		BMI (kg/m2)	0.18	0.21	0.02	0.20	-0.01	0.37	0.56	-0.17	0.59	-0.01
		PATE	-0.02	0.01	-0.05	0.02	0.65	-0.04	-0.02	-0.03	-0.01	0.89

Bivariate correlations between PATE and twins' weight, height or BMI are all between 0.0 and -.09 and suggest that there is no relationship between parental attitudes towards eating and their children's weight status. However, the twin correlation for PATE is very high (r=.91 at 3 years and r=.90 at age 4 for the total sample; not shown in Table 8.5) suggesting that parents tend to relate their attitudes towards feeding to both twins in a similar way. In addition, when splitting the sample by zygosity, the correlations were very similar for MZ (r=.94) and DZ (r=.89) twins suggesting that parent feeding attitudes are a source of substantial shared environmental influence. It is also possible that rater bias might partly explain the high similarity in correlations since parents do not differentiate between their children in their feeding behaviour.

In order to investigate differences in parent feeding style in overweight children, overweight twins at the top 10% of the distribution for weight were compared to the rest of the distribution. The mean comparisons between overweight and normal weight twins on measures of parent feeding style (PATE) are shown in Table 8.6. Analyses of variance (ANOVA) were applied to the data to test the significance of mean differences between the groups. The ANOVA results show that there were no significant differences between the groups at age 3 years ($F(1, 4614)=7.62$, $p=.01$). At age four, overweight children scored significantly lower on PATE in comparison to normal weight children ($F(1, 4614)=14.97$, $p=.000$), however the effect size is small. The fact that mean differences on parental attitudes towards eating exist between overweight and normal weight children at age 4 years, suggests that parents of overweight children are somewhat less controlling over their children's eating habits.

Pearson correlations for PATE were the same for both groups at ages 3 and 4 years (r=.91) and indicate that overweight and normal weight children are treated very similarly in terms of parental feeding behaviour. Overall, these results

do not suggest that differences in parent feeding style are associated with overweight in young children.

Table 8.6 Comparison of mean scores for parent attitudes towards eating (PATE) between overweight and normal weight children by analysis of variance (ANOVA) at ages 3 and 4 years.

PATE	***Descriptive Statistics***			***ANOVA***	
	N	***Mean***	***SD***	***F (1, 4614)***	***p***
3 years					
normal weight	4168	0.01	0.99	7.62	0.01
overweight	448	-0.12	1.04		
4 years					
normal weight	4164	0.02	0.99	14.97	0.00
overweight	452	-0.17	1.05		

Nevertheless, it is possible that a link exists between maternal weight and the way mothers feed their children irrespective of whether the child is currently overweight or not. For instance, overweight mothers might differ in their feeding style from normal weight mothers because of concerns that their children might also become overweight in the future (i.e. feeding style as a function of maternal weight status rather than child's weight status).

To investigate this link, the relationship between maternal weight status and attitudes towards their twins' eating was explored. A total of 2086 mothers reported on their heights and weights and their BMIs were calculated. The sample was divided into a group of normal weight mothers (N=1846 ; BMI <28.5 kg/m^2) and overweight/obese mothers (N=240, BMI>= 28.5 kg/m^2). Analysis of variance revealed that at both ages there were no significant mean differences between overweight and normal weight mothers for the PATE total score (age 3 years: $F(1, 2084)=.612$, $p=.43$; age 4 years: $F(1, 2084)=.007$, $p=.93$). This finding suggests that normal weight and overweight/obese mothers are similar in the way they feed their children.

In addition, no significant mean differences in feeding style were found for twin pairs with substantial within pair differences in body weight. Weight discordant twin pairs were selected according to their absolute weight difference within twin pairs (see Fig 8.1). 197 and 276 twin pairs with an absolute weight difference of at least 3 kg were selected as weight discordant pairs at ages 3 and 4 years respectively. At both ages mean scores for parent feeding style were calculated for each twin and differences were formally tested using analysis of variance. A comparison of mean scores between heavier and lighter twins resulted in no significant differences for parental feeding style at age 3 years ($F(1, 392)=1.82$, $p=.18$) and at age 4 years ($F(1, 550)=3.52$, $p=.06$). Furthermore, no significant differences emerged when the sample was divided by gender and zygosity.

These findings suggest that parents of young twins tend to treat their children similarly in respect of their feeding style. This effect seems to be independent of parents' own weight, their children's weight as well as of gender and zygosity.

Relationship between children's weight and developmental measures

In order to assess potential developmental correlates linked to childhood obesity, the relationship between language, non-verbal cognitive development and behaviour problems was investigated.

Table 8.7 summarises the standardised means and standard deviations of all developmental assessments for overweight and normal weight twins at ages 3 and 4 years. Analyses of variance were applied to the data and suggest that mean differences between the groups are small and not statistically significant for any of the measures.

Table 8.7: Results of Analyses of Variance for mean differences between normal weight (<90th percentile) and overweight (>=90th percentile) children for behaviour problems, language and non verbal cognitive development at ages 3 and 4 years; after exclusions on developmental measures, the total number of twins was N=3784

			Descriptive Statistics			***ANOVA***	
			N	***Mean***	***SD***	***F***	***p***
Behaviour Problems (RRPSPC)	**3 year**	**normal weight**	3394	0.00	1.00	0.00	0.958
		overweight	390	0.00	1.02		
	4 year	**normal weight**	3404	-0.01	0.99	0.87	0.351
		overweight	380	0.05	1.08		
Language (MCDI)	**3 year**	**normal weight**	3394	0.00	1.00	0.32	0.574
		overweight	390	0.03	0.98		
	4 year	**normal weight**	3404	0.00	0.99	0.98	0.323
		overweight	380	0.03	1.08		
Non-verbal cognitive ability (PARCA)	**3 year**	**normal weight**	3394	-0.01	1.00	1.01	0.315
		overweight	390	0.05	1.01		
	4 year	**normal weight**	3404	0.01	1.00	0.27	0.601
		overweight	380	-0.05	1.02		

In addition, phenotypic correlations between weight and developmental measures were calculated and are summarised in Table 8.8. There are only weak associations between weight, language ability (MCDI), non-verbal cognitive ability (PARCA) and behaviour problems (RRPSPC). All the correlations between weight and developmental measures are small and insignificant (p>.001) ranging from -.01 to .05. These findings suggest that shared links between development and body weight are unlikely to exist as the phenotypic correlations were weak and not statistically significant.

Table 8.8: Phenotypic correlations between weight (corrected for height), behaviour problems (RRPSPC), language (MCDI) and non verbal cognitive development (PARCA) at ages 3 and 4 years; N=3784

	Body Weight	
	3 years	***4 years***
Behaviour Problems	0.01	0.02
Language	0.01	0.05
Non-verbal	-0.01	0.02

8.5 Conclusion

The current results provide evidence that genetic factors contribute to the familial resemblance of weight and overweight. However, the findings also show that a substantial proportion of the variance in weight is accounted for by shared as well as non-shared environmental factors. Since family environments seem to be important for the development of food preferences, patterns of food intake, eating styles, especially during early childhood, the effect of parent feeding style on children's body weight was observed. Although parental feeding constitutes shared family environment, this factor was not associated with twins' or maternal weight status. Furthermore, there were no links between developmental measures

(i.e. verbal and non-verbal cognitive development, behaviour problems) and children's weight status.

The univariate results on weight and overweight in children support the QTL theory that weight is distributed quantitatively as a dimension and that overweight is the quantitative extreme of the same distribution rather than representing an aetiologically distinct disorder. Although several single-gene disorders such as Prader-Willi include obesity as one of several pleiotropic symptoms, these are rare mutations that have little effect on the population distribution of weight (Barsh, Farooqi, & O'Rahilly, 2000). The QTL perspective has implications for design and analysis of molecular genetic studies because, if multiple genes affect weight and overweight, each gene is likely to be of small effect size. For this reason, molecular genetic designs are needed that have the power to detect QTLs of small effect size (Risch, 2000; Risch & Merikangas, 1996). The definitive test of the QTL hypothesis will come when genes are identified that are associated with obesity. The QTL prediction is that genes associated with overweight will also be associated with variation in weight throughout the normal distribution.

A broader implication of a QTL perspective is that there may be no unique mechanisms for obesity if the genetic and environmental mechanisms responsible for overweight are also responsible for the normal range of variation in weight. For example, in studying the developmental pathways by which vulnerable genotypes become obese phenotypes, it is unlikely that any single genetic mechanism causes obesity. It is more likely that genetic variation in multiple pathways from genes to behaviour make small probabilistic contributions to the likelihood of obesity, although any single QTL could provide a discrete window through which to view one of these mechanisms as it interacts with other processes.

Another implication of the genetic link between weight and overweight is that treatments for obesity may also be effective in reducing weight in the normal range and vice versa. This may be important from a public health perspective. Rather than aiming for dramatic and expensive interventions that cure obese individuals, inexpensive interventions that have only a small effect on many individuals can nonetheless greatly reduce population-wide financial burden, health risks and impact on quality of life associated with the obesity epidemic (Kopelman, 2000). Targeting interventions for children at genetic risk before they become obese and incur medical and social collateral damage may be the most important reason for identifying QTLs for weight and overweight (Dietz, 1994; Kotani et al., 1997; Must & Strauss, 1999).

The most far-reaching implication of a QTL perspective is conceptual. A common mistake is to think that all people are the same genetically except for a few rogue mutations that lead to disorders such as obesity. In contrast, the QTL perspective suggests that genetic variation is normal and pandemic. Many genes affect most complex traits and, together with environmental variation, these QTLs are responsible for normal variation as well as for the abnormal extremes of these quantitative traits. In this way, a QTL perspective blurs the aetiological boundaries between the normal and the abnormal. In other words, we all have many alleles that contribute to overweight but some of us are unlucky in the hand that we draw at conception from our parents' genetic decks of cards.

In the present study, heritability estimates were similar for boys and girls and little evidence for sex-specific genetic effects emerged. Although some twin studies have reported different genetic estimates for men and women (Harris, Tambs, & Magnus, 1995; Herskind, McGue, Sorensen, & Harvald, 1996; Pietilainen et al., 1999), the reported differences are neither large nor consistent.

It should be emphasised that finding genetic influence on weight and overweight does not mean that the environment is unimportant. The present results suggest that environmental influences on body weight are substantial. However, unlike results for adults, the current findings suggest that a considerable amount of environmental variance is shared by siblings growing up in the same family for both weight and overweight. One possible example of environmental influence on children's weight is their parents' feeding style and their attitudes towards children's diet. Because the twin correlations on parent feeding style were very high and virtually identical for MZ and DZ twin pair, the results provide evidence that parental attitudes towards their children's eating constitute a source of shared environment. However, the results also indicate that this factor is unlikely to be contributing to differences in weight as the phenotypic correlations between parent feeding style and children's weight were near zero. It is therefore likely that shared environmental influences other than parent feeding styles are linked to children's weight. These factors might include diet, children's eating habits, food preferences and lifestyles.

Putting the results for children together with other results for adults suggests that although the environment has important effects on weight and overweight in childhood, in the long run environmental influences are non-shared. Environmental influences are also responsible for the dramatic rise in weight and overweight during the past few decades as countries shift from dietary deficit to dietary excess (Kopelman, 2000; World Health Organization, 2003). This secular increase cannot be explained by genetic factors *per se*.

Limitations of the study include general limitations of the twin method, the use of parent-reported weight, and the use of the tenth percentile as a criterion for the overweight group. Although the twin method has been vigorously defended as "the perfect natural experiment" (Martin, Boomsma, & Machin, 1997), the method is not without problems. Some problems are conservative from a genetic perspective in

that, if true, they make MZ twins less similar than they would otherwise have been, thus lowering estimates of heritability. For example, it has been alleged that the atypical gestation of MZ twins causes increased rates of disorder (Phillips, 1993), although other studies indicate that this is not the case (Christensen, Vaupel, Holmn, & Yashlin, 1995). A recent report on the influence of zygosity and chorionicity on body fat distribution suggests that the chorion type of MZ twins does not bias the twin design and the estimation of the genetic contribution to body weight in adulthood (Loos, Beunen, Fagard, Derom, & Vlietinck, 2001).

Some problems might inflate heritability estimates, most notably, the possibility that MZ twins share more similar postnatal environments than DZ twins, although it appears that this is not usually the cause of their greater phenotypic similarity but rather the consequence of their genetic identity (also see Chapter 3 for a more detailed discussion of the EEA).

Concerning the use of parent reports of children's weight and height, Wardle and colleagues (Wardle, Guthrie, Sanderson, Birch, & Plomin, 2001; Wardle, Sanderson, Guthrie, Rapoport, & Plomin, 2002) studied a subsample of TEDS twins consisting of 428 children who were visited in their homes at 4 years of age and children's weight and height were measured. The correlation between parent-reported weight and the children's measured weight was .77 suggesting adequate reliability for parent reported weight. Other studies have also shown that parent reports of their young children's weight are reasonably valid (Reed & Price, 1998). The use of parent reports made it impossible to assess body fat distribution such as subscapular/triceps ratio. However, multivariate genetic research suggests that genetic influences on body fat distribution are substantially independent of genetic influences on overall obesity both in children (Faith et al., 1999) and adults (Cardon, Carmelli, Fabsitz, & Reed, 1994).

Another limitation is the use of the tenth percentile as a selection criterion of the overweight group. This criterion may be used as a marker to identify children

'at risk' for later obesity. However, results might differ if a more severely overweight group of children were selected. Although, there are no general criteria for diagnosing obesity in children (Flegal, Ogden, Wei, Kuczmarski, & Johnson, 2001; Reilly, 1998), the 85th and the 95th percentile have been suggested as target reference points for assessing overweight risk and severe overweight in children (American Obesity Association, 2003).

Although there have been considerable advances on the molecular genetics of finding candidate genes related to overweight and obesity (Hebebrand, Sommerlad, Geller, Gorg, & Hinney, 2001; Boutin & Froguel, 2001), behavioural genetic methods have as yet provided relatively little information towards widening the present understanding on the environmental influences and intermediate behaviours which contribute to human obesity. Since human obesity is, in part, environmentally mediated it is important to identify genetic-environmental interactions and certain "candidate" behaviours and environments related to eating and physical activity early on.

Effects of shared environment on body weight are small and have only been found in a minority of twin studies using younger samples (Grilo et al., 1991). It is therefore possible that different genes and environments may be important for weight at different ages. Nonshared environments appear to account for a substantial proportion of the population variance in overweight but remain largely unspecified and unmeasured. One of the future challenges for obesity research is to identify these environments. Food preferences are influenced early by parental eating habits, and when developed in childhood, they tend to remain fairly constant into adulthood (Birch & Davison, 2001; Tibbs et al., 2001). In addition, physical activity (or more commonly, physical inactivity) habits in parents are related to their children's levels of activity (Fogelholm, Nuutinen, Pasanen, Myohanen, & Sateela, 1999). A recent report on food preferences for subsample of TEDS twins found

differences in food preferences between children of obese parents and those of lean parents (Wardle et al., 2001).

The current results should be viewed with some caution as to the generalisation from the parent feeding style measure used. Due to the large sample size of TEDS and to considerations of cost it was not possible to include a more comprehensive questionnaire on parental feeding behaviours in the 3- and 4-year booklets, for instance to differentiate between parent encouragement and control over eating. As mentioned earlier, a more detailed study exists on a subsample of 214 twin pairs from TEDS which investigated differences in parental feeding styles between children from obese and from lean families (Wardle et al., 2002). The study included a more complete range of parental feeding measures and found that the correlations for maternal control over eating, prompting, emotional and instrumental use of food were very high and virtually the same for MZ and DZ twins. The findings reported in this dissertation are based on the total TEDS sample and are very similar to the results reported by Wardle and colleagues (2002) despite the limited number of questions asked on parental feeding styles. Therefore, the present findings suggest that parental feeding styles constitute shared environmental influences that contribute relatively little towards weight differences in preschoolers.

It is likely that environmental factors other than parental feeding behaviours are more influential in determining body weight in children. It is possible that the environmental factors involved in the aetiology of overweight and obesity are linked to food preferences as well as levels of physical activity and inactivity. Behavioural genetics holds the tools to investigate and identify such links. Future studies are needed which target the behavioural intermediaries that promote overweight such as the factors that shape activity patterns, meals taken away from home, the impact of stress on family members' eating styles and weight gain. Because childhood overweight and later obesity are multifactorial problems, further

studies are needed to test hypotheses and develop theoretical models describing how environmental factors and behavioural intermediaries can work in concert with genetic predispositions to promote the development of obesity.

In conclusion, overweight, not just normal variation in weight is highly heritable in young children. Moreover, the heritabilities of weight and overweight are similar and DF extremes analyses suggest that weight and overweight are linked genetically. In other words, overweight appears to be merely the quantitative extreme of the genetic factors responsible for normal variation in weight as assumed by QTL theory.

Although behavioural genetic research on overweight and obesity has provided estimates of the proportion of the variance in a population accounted for by genetic factors, more research is needed to delineate how genetics and environmental factors interact in the aetiology of childhood obesity. Addressing this question will remain especially challenging because parents provide both genes and environment for children. The present findings reveal a complex relationship between family environment, parental behaviours and children's weight status.

8.6 Acknowledgements

Parts of this chapter originate from a published manuscript, for which I thank the co-authors:

Koeppen-Schomerus, G., Wardle, J., & Plomin, R. (2001). A genetic analysis of weight and overweight in 4-year-old twin pairs. International Journal of Obesity & Related Metabolic Disorders, 25, 838-844.

9 Otitis Media

9.1 Overview

Although theories of the origins of otitis media (OM) usually focus on shared family environment, two previous twin studies suggest a strong genetic component (Kvaerner et al., 1997; Casselbrant et al., 1999). However, these studies relied on retrospective self-reports in adulthood (Kvaerner et al., 1997) or were based on a relatively small clinical sample (Casselbrant et al., 1999). The TEDS sample proffers the opportunity to assess the contributions of genetic and environmental factors towards OM prospectively in a population sample of young twins.

From a developmental perspective, there is some evidence that prolonged and frequent episodes of OM in children are associated with developmental deficits (Paradise et al., 2000; Shriberg et al., 2000; Vernon-Feagans et al., 1996). However, next to nothing is known about the mechanisms through which such associations are mediated.

In this chapter the genetic and environmental contributions towards individual differences in OM symptoms as well as in the 10% of children with the most extreme symptoms will be assessed at 1.5, 3 and 4 years of age. In addition, the relationship between OM with language, non-verbal cognitive development and behaviour problems will be evaluated and the genetic and environmental mechanisms for any significant associations will be explored.

9.2 Introduction:

As outlined in Chapter 2, otitis media (OM) is one of the most common diseases in childhood. Much is known of the epidemiology, natural course, diagnosis, sequelae and risk factors of both the acute form (AOM) and the

persistent secretory form, otitis media with effusion (OME). Environmental contributors that have been emphasised in relation to OM are day care attendance (Rovers, Zielhuis, Ingels, & van der Wilt, 1999; Paradise et al., 1997), the number of siblings (Dewey et al., 2000), and housing conditions (Rylander & Megevand, 2000; Birch & Elbrond, 1987), which are examples of shared environmental factors because they are largely shared by children growing up in the same family (Plomin et al., 2001).

The influence of genetics on OM has received considerably less attention, probably because it is a transient and relatively benign disease of childhood. However, knowledge of this heritability, and especially knowledge of the link between heritability and particular risk factors, could aid the development of environmental interventions. This information could also eventually facilitate the early prediction of the persistence or transience of the condition in at-risk populations.

Current management of OM restricts surgical intervention to those cases with severe and persistent OME. However, during the lengthy period in which frequency and severity of the condition are assessed, the child may experience developmental delays due to his/her impaired hearing.

In addition to needing more research on the extent to which OM leads to developmental problems, next to nothing is known about the aetiology of such links between OM and development. This lack of research may be due to the reasonable assumption that OM causes such correlations. For example, OM-induced hearing impairment can affect children's ability to interpret subtle environmental clues that play an important role in everyday learning processes and especially language. However, rather than assuming that such correlations are causally linked, it is necessary to formally test this association.

For example, because genetic vulnerabilities are so important for OM, it is possible that the same genetic factors that affect OM vulnerability are also

responsible for causing problems in language or cognitive development. Understanding the origins of OM-related developmental problems is likely to have implications for prevention and intervention.

9.3 Study Objectives:

The aims of this study were to assess the contributions of genetic and environmental factors towards otitis media longitudinally and to investigate associations with developmental measures at ages 1.5, 3 and 4 years.

Using univariate analyses, genetic and environmental influences were investigated for individual items as well as for the OM total score for the complete sample as well as for the top 10% of the distribution applying DF extremes analyses. In line with past reports (Casselbrant et al., 1999; Kvaerner et al., 1997), heritability was expected to be substantial whereas the effects of shared environment will be moderate. Sex differences in aetiology were also tested for individual items and OM total scores using a standard model fitting approach (Neale et al., 1992).

Multivariate analyses were used to assess the strength of links between OM, cognitive and language development and behaviour problems. The genetic and environmental aetiology of correlations between OM and developmental measures was also investigated. It was hypothesised that OM would be most strongly associated with language development, then with nonverbal cognitive ability and less strongly with behaviour problems. If significant links were found, multivariate genetic techniques were used to investigate their genetic and environmental aetiologies.

Due to the substantial familial component of OM, the expected finding was that the relationship between OM and these developmental domains would reflect common genetic influences rather than shared environmental influences in common between them.

9.4 Sample:

The initial sample included 3910 families who completed the background booklet (when the twins were 1.5 years old), the 2-year, 3-year and the 4-year booklet (see Chapter 5 for further details on the sample). For 116 families the twins' hearing measures were incomplete or missing (7 families at age 1.5 years, 52 families at age 3 years, and 57 families at age 4 years) and they were therefore excluded from the analyses. Twins' zygosity status could not be determined for 7 families and they were also excluded.

The final sample included 3787 eligible families with available data on otitis media measures, consisting of 1297 monozygotic (MZ), 1268 dizygotic same sex (DZss) and 1222 dizygotic opposite sex (DZos) twin pairs.

Multivariate analyses include all twins with complete data on the OM as well as on the developmental measures (MCDI, PARCA and RRSPCP, see Chapter 5 for details) at 2, 3 and 4 years. In total there were 1475 eligible same-sex twin pairs; 760 were monozygotic (MZ) and 715 were dizygotic (DZ).

A comparison of the sample used for the initial univariate analyses to the sample used for multivariate analyses shows that the samples are similar (see Table 9.1).

Table 9.1 Sample comparisons between families with complete data on OM at all ages of assessment (univariate sample) and families with complete data on OM and developmental outcome measures at all three ages of assessment (multivariate sample).

		Univariate sample N=3787		**Multivariate sample** N=1475	
		%	**95% CI**	**%**	**95% CI**
Ethnicity	**white/caucasian**	94.4	94.2-94.6	94.4	94.2-94.6
	other	5.6	1.6-8.6	5.6	1.6-8.6
Father's Social Class					
I	**Professional**	11.9	9.1-14.7	13.6	9.0-18.2
II	**Managerial and technical**	31.7	29.5-33.9	30.2	21.1-39.3
IIIN	**Skilled - non-manual**	8.4	5.5-11.3	8.3	2.2-14.4
IIIM	**Skilled - manual**	24.2	21.8-26.6	23.7	18.6-28.8
IV	**Partly skilled**	6.0	3.0-9.0	6.2	-.1-12.5
V	**unskilled**	2.7	-.04-5.8	2.0	-4.6-8.6
Missing		15.0	12.3-17.7	15.4	10.0-20.8

9.5 Measures:

Details on the measures used for the present analyses have already been described (see Chapter 5).

Otitis media was assessed at ages 1.5, 3 and 4 years using a composite scale consisting of 7 items at age 1.5 years and 6 items at ages 3 and 4 years.

Developmental assessments included language development (MCDI), non-verbal cognitive development (PARCA) and behaviour problems (RRPSPC) assessed at ages 2, 3 and 4 years. At each age, the measures were standardised individually to zero mean and unit variance. All measures were corrected for the effects of age and sex.

9.6 Analyses:

9.6.1 Univariate analyses:

Statistical analyses are reported, on twins with valid data on OM symptoms at ages 1.5, 3 and 4 years. To allow the assessment of sex differences, a

heterogeneity analysis was performed to test whether the genetic architecture of otitis media symptoms was different in males and females. Models including additive genetic effects and common and specific environmental factors were fitted to the data with parameters alternatively set equal or allowed to differ for both genders. Variance-covariance matrices were used to formally test the data by applying a univariate ACE model using the software package MX (Neale, 1997).

DF analyses (DeFries et al., 1985; DeFries et al., 1988) were applied to assess group heritability for those children with the most extreme OM symptoms in relation to the entire distribution. Probands falling at or above the 90th percentile of the distribution of the OM scales were selected and compared with the scores of their co-twins at each age.

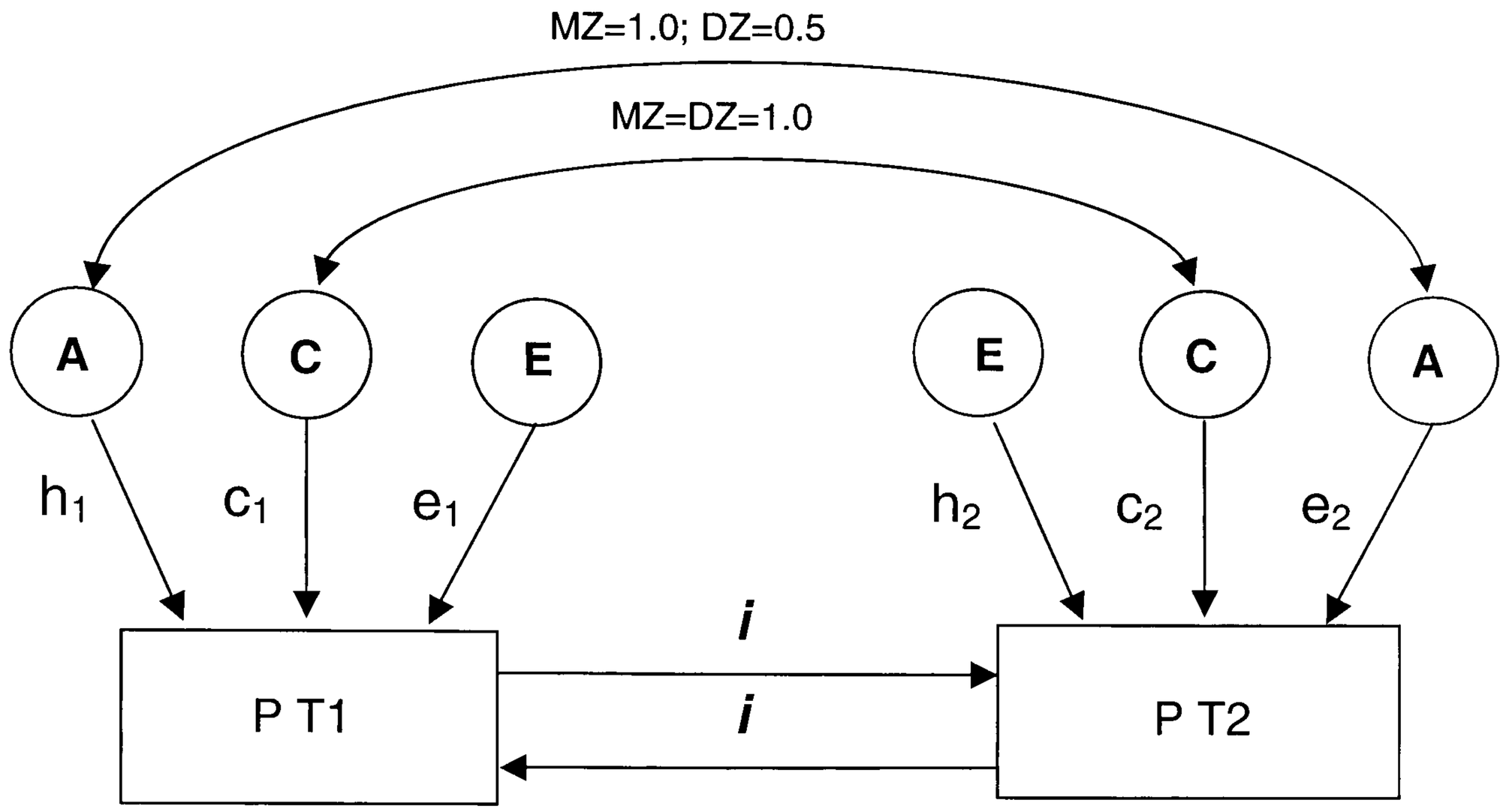
Further details of these analyses are given in Chapter 3.

9.6.2 Reciprocal Sibling Interaction

As part of the aetiology of otitis media is related to infections, the possibility of disease transmission from one twin to another was taken into consideration.

A phenotypic sibling interaction model (PACE) was used to assess potential effects of interaction between siblings for the occurrence of otitis media. The figure below (Fig. 9.1) shows a path diagram of the PACE model which is an extension of the basic univariate ACE model for twins and includes an additional path (*i*) from each twin's phenotype (P T1) to that of their co-twin's (P T2). This path *i* accounts for effects of phenotypic interaction between siblings. If *i* is positive there is evidence for a two-way interaction between twins, i.e. the more a twin is affected by OM related symptoms the more the co-twin will be affected as a direct consequence of this influence.

Figure 9.1 PACE model for univariate twin data incorporating reciprocal interaction between siblings.



Paths for additive genetic (A), shared environmental (C) and non-shared environmental (E) factors for a given phenotype (P) between twins (T1 and T2). Path *i* assesses the direct phenotypic effects of a twin on his or her co-twin. Diagram adapted from Neale (1999)

9.6.3 Multivariate analyses:

As explained earlier (see Chapter 3), multivariate genetic analysis addresses the genetic and environmental origins of the phenotypic overlap between two dimensions or disorders rather than considering the aetiology of each separately as in univariate analysis. Multivariate genetic analyses were used to assess whether and to what extent any significant associations between OM and developmental measures (i.e. language, non-verbal cognitive development and behaviour problems) were mediated by the same genetic factors.

9.7 Results

9.7.1 Univariate analyses:

Univariate intraclass correlations for individual items and otitis media (OM) total score were calculated according to zygosity and sex and are summarised in Table 9.2. Overall, the correlations for MZ twins are consistently and considerably

higher as compared to DZ twins suggesting substantial genetic influence for individual items as well as for the total OM score. Sex differences in the twin correlations are small. The twin correlations for opposite-sex pairs are somewhat lower than those for same-sex DZ pairs for some of the OM items, suggesting the possibility of sex-specific genetic or environmental influences on susceptibility to OM. However, for the OM total scores the overlapping confidence intervals in correlations between same-sex and opposite-sex twins as between males and females indicate that there are no significant sex differences at any age of assessment.

Table 9.2 Twin correlations (and 95% confidence intervals) for twin pairs with complete data on OM scales at ages 1.5 years, 3 years and 4 years by zygosity and sex.

	1.5 years					3 Years					4 Years				
	MZ		DZ			MZ		DZ			MZ		DZ		
	male[1]	female[2]	male[3]	female[4]	os[5]	male[1]	female[2]	male[3]	female[4]	os[5]	male[1]	female[2]	male[3]	female[4]	os[5]
Items															
Catarrh during cold	.98	.97	.81	.83	.85	.93	.96	.71	.72	.71	.92	.92	.63	.70	.68
95% CI	.98-.99	.97-.98	.79-.83	.81-.86	.83-.87	.92-.94	.96-.97	.67-.75	.68-.77	.68-.74	.91-.94	.91-.93	.58-.68	.67-.75	.65-.72
Hearing difficulty*	.89	.72	.64	.61	.52										
95% CI	.88-.91	.86-.89	.60-.68	.56-.67	.48-.56	---	---	---	---	---	---	---	---	---	---
Ignores people*	---	---	---	---	---	.90	.93	.63	.71	.68	.90	.92	.57	.65	.62
95% CI						.89-.92	.92-.94	.58-.68	.67-.76	.65-.72	.89-.92	.91-.93	.52-.62	.61-.70	.59-.66
Breathes through mouth	.94	.86	.61	.63	.58	.86	.84	.41	.53	.49	.86	.83	.40	.50	.39
95% CI	.93-.95	.84-.88	.56-.67	.58-.68	.55-.62	.84-.88	.82-.86	.35-.47	.47-.59	.45-.53	.84-.88	.81-.86	.34-.46	.44-.56	.35-44
Snores or snorts in sleep	.74	.79	.37	.53	.35	.77	.70	.26	.33	.21	.81	.75	.30	.34	.24
95% CI	.71-.78	.76-.82	.31-.44	.47-.59	.31-.40	.74-.80	.67-.74	.19-.33	.26-.40	.16-.27	.79-.84	.72-.79	.23-.38	.27-.41	.19-.29
Ears leaked pus or mucus	.70	.63	.56	.41	.45	.75	.60	.34	.31	.43	.76	.70	.42	.39	.36
95% CI	.67-.75	.59-.68	.51-.62	.35-.47	.41-.50	.72-.79	.56-.65	.28-.41	.24-.38	.38-.48	.73-.80	.67-.74	.36-.48	.32-.46	.31-.41
Pulls or scratches ears*	.78	.79	.53	.59	.49										
95% CI	.75-.82	.76-.82	.47-.59	.54-.65	.45-.53	---	---	---	---	---	---	---	---	---	---
Red or sore ears*	.84	.89	.65	.62	.60										
95% CI	.88-.91	.88-.91	.61-.70	.58-.66	.57-.64	---	---	---	---	---	---	---	---	---	---
Earache*	---	---	---	---	---	.79	.78	.51	.59	.50	.80	.74	.51	.46	.46
95% CI						.77-.82	.76-.81	.46-.57	.54-.65	.46-.55	.78-.83	.71-.78	.46-.57	.40-.53	.42-.50
TOTAL SCORE	**.89**	**.87**	**.67**	**.66**	**.61**	**.85**	**.88**	**.46**	**.53**	**.55**	**.88**	**.85**	**.46**	**.54**	**.51**
	.88-.91	**.86-.89**	**.63-.72**	**.62-.71**	**.58-.65**	**.83-.88**	**.86-.90**	**.40-.52**	**.47-.59**	**.51-.59**	**.86-.90**	**.83-.88**	**.40-.52**	**.48-.60**	**.47-.56**

[1]MZ male: N_{pairs}=597
[2]MZ female: N_{pairs}=700
[3]DZ male: N_{pairs}=652
[4]DZ female: N_{pairs}=616
[5]DZ opposite sex: N_{pairs}=1222
* incomplete rows reflect the different questions asked at age 1.5 versus ages 3 and 4 years

For univariate analyses, structural equation models were applied to the variance/ covariance matrices to estimate the contribution of additive genetic factors (a^2), shared environment (c^2), and unique environment (e^2) to the phenotypic variance. Estimates and fit statistics for individual items as well as the OM total score are summarised in Table 9.3. At 1.5 years, there are differences between males and females for most items with somewhat higher heritability estimates in males. Subsequently, at ages 3 and 4 years these gender differences become less pronounced. There are no significant sex differences on the OM total score at any age of assessment. For the OM total score heritability increases from 0.48 to 0.69 between the ages of 1.5 and 3 years, while shared environment decreases from 0.41 to 0.18. At 4 years of age the estimates remain relatively stable (a^2=.71 ; c^2=.15).

Furthermore, an examination of the results for the individual items in Table 9.3 suggests that items related to acute infection (i.e. catarrh, earache, ears leak pus or mucus, pulls or scratches ears, red or sore ears) tend to show lower heritability on average (40%, 52% and 55% at ages 1.5, 3 and 4 years respectively) and greater shared environment (51%, 29% and 19 % at respective ages) than the items related to chronic airway blockage (i.e. breathes through mouth, snores or snorts in sleep) with average heritabilities of 62%, 75% and 78% and average shared environment estimates of 22%, 4% and 3% at ages 1.5, 3 and 4 years respectively. Also, for both domains as well as for the OM total score heritability increases with age whereas the effect of shared environment decreases.

ıble 9.3: Univariate results and model of best fit for otitis media (OM) total score and individual items: estimates of additive genes (a^2), shared environment (c^2) and non-shared environment (e^2) at ages 1.5, 3 and 4 years.

1.5 years	Model Fit Statistics				
Item	X^2	df	p	AIC	RMSEA
Catarrh during cold	7.17	8	.52	-8.83	.000
Hearing difficulty	39.33	8	.00	23.33	.035
Breathes through mouth	21.78	8	.01	3.78	.017
Snores or snorts in sleep	7.12	8	.52	-8.88	.004
Ears leaked pus or mucus	98.86	8	.00	82.86	.067
Pulls or scratches ears	16.48	12	.17	-7.52	.008
Red or sore ears	38.22	8	.00	22.22	.039
OM TOTAL score	**15.13**	**12**	**.23**	**-8.87**	**.000**

1.5 years	Common effects model			Sex differences model					
				males			**females**		
Item (95% CI)	a^2	c^2	e^2	a^2	c^2	e^2	a^2	c^2	e^2
Catarrh during cold	---	---	---	.32 (.29-.36)	.66 (.62-.69)	.02 (.02-.02)	.25 (.21-.28)	.72 (.69-.76)	.03 (.03-.03)
Hearing difficulty	---	---	---	.48 (.40-.56)	.41 (.32-.48)	.11 (.10-.13)	.38 (.27-.48)	.35 (.25-.44)	.27 (.24-.30)
Breathes through mouth	---	---	---	.74 (.68-.80)	.21 (.15-.27)	.05 (.04-.06)	.46 (.37-.56)	.39 (.30-.48)	.15 (.13-.16)
Snores or snorts in sleep	---	---	---	.75 (.64-.78)	.00 (.00-.11)	.25 (.22-.28)	.53 (.42-.64)	.27 (.15-.36)	.21 (.19-.23)
Ears leaked pus or mucus	---	---	---	.33 (.21-.44)	.33 (.23-.43)	.34 (.31-.38)	.46 (.36-.55)	.17 (.10-.24)	.37 (.33-.42)
Pulls or scratches ears	.54 (.48-.60)	.25 (.19-.30)	.22 (.20-.23)	---	---	---	---	---	---
Red or sore ears	---	---	---	.39 (.31-.48)	.44 (.35-.52)	.17 (.15-.19)	.61 (.53-.67)	.28 (.22-.36)	.11 (.10-.12)
OM TOTAL score	**.48 (.44-.52)**	**.41 (.36-.45)**	**.12 (.11-.13)**	**---**	**---**	**---**	**---**	**---**	**---**

(Table 9.3 continued)

3 years	Model Fit Statistics				
Item	X^2	df	p	AIC	RMSEA
Catarrh during cold	28.85	12	.00	4.85	.023
Ignores people	22.80	12	.03	-1.21	.018
Breathes through mouth	35.68	12	.00	11.68	.032
Snores or snorts in sleep	86.06	12	.00	62.06	.055
Ears leaked pus or mucus	38.27	8	.03	20.27	.034
Earache	17.57	12	.13	-6.43	.004
TOTAL score	**22.70**	**12**	**.03**	**-1.30**	**.001**

3 years	Common effects model			Sex differences model					
				males			females		
Item (95% CI)	a^2	c^2	e^2	a^2	c^2	e^2	a^2	c^2	e^2
Catarrh during cold	.46(.43-.50)	.49 (.45-.52)	.05 (.05-.06)	---	---	---	---	---	---
Ignores people	.47 (.44-.54)	.45 (.40-.48)	.08 (.07-.09)	---	---	---	---	---	---
Breathes through mouth	.78 (.72-.84)	.08(.01-.13)	.14 (.13-.16)	---	---	---	---	---	---
Snores or snorts in sleep	.73 (.71-.76)	.00 (.00-.01)	.27 (.24-.29)	---	---	---	---	---	---
Ears leaked pus or mucus	---	---	---	.60 (.50-.70)	.10 (.02-.20)	.30 (.27-.34)	.51 (.40-.60)	.09 (.02-.18)	.40 (.36-.44)
Earache	.50 (.44-.56)	.28(.22-.33)	.22 (.21-.24)	---	---	---	---	---	---
OM TOTAL score	**.69 (.63-.74)**	**.18 (.13-.23)**	**.13 (.12-.14)**	**---**	**---**	**---**	**---**	**---**	**---**

(Table 9.3 continued)

4 years	Model Fit Statistics				
Item	X^2	df	p	AIC	RMSEA
Catarrh during cold	10.89	12	.54	-13.11	.003
Ignores people	19.38	12	.08	-4.62	.011
Breathes through mouth	19.26	8	.01	3.26	.014
Snores or snorts in sleep	30.00	8	.00	14.00	.030
Ears leaked pus or mucus	47.94	8	.00	31.94	.039
Earache	15.23	12	.23	-8.77	.000
OM TOTAL score	**18.27**	**12**	**.11**	**-5.73**	**.001**

4 years	Common effects model			Sex differences model					
				males			females		
Item (95% CI)	a^2	c^2	e^2	a^2	c^2	e^2	a^2	c^2	e^2
Catarrh during cold	.51(.47-.55)	.41 (.37-.45)	.08 (.07-.08)	---	---	---	---	---	---
Ignores people	.55 (.51-.60)	.35 (.30-.39)	.10 (.10-.11)	---	---	---	---	---	---
Breathes through mouth	---	---	---	.87 (.80-.88)	.00 (.00-.07)	.13 (.12-.15)	.71 (.61-.83)	.12 (.00-.23)	.17 (.15-.19)
Snores or snorts in sleep	---	---	---	.82 (.79-.84)	.00 (.00-.03)	.18 (.16-.21)	.76 (.69-.79)	.01 (.00-.07)	.24 (.21-.27)
Ears leaked pus or mucus	---	---	---	.61 (.49-.72)	.12 (.02-.22)	.27 (.25-.31)	.47 (.36-.55)	.06 (.00-.14)	.47 (.43-.52)
Earache	.60 (.53-.67)	.17(.11-.23)	.23 (.22-.25)	---	---	---	---	---	---
OM TOTAL score	**.71 (.65-.77)**	**.15 (.10-.21)**	**.14 (.13-.15)**	**---**	**---**	**---**	**---**	**---**	**---**

A phenotypic sibling interaction model (PACE) was used to account for potential interactive effects between twin and co-twin. The PACE model was applied to the OM total score data and provided results similar to the ACE models. However, the sibling interaction tem was found to be negative and non-significant at all ages (-.21 at 1.5 years, -.17 at 3 years and -.02. at age 4).

DF analyses were used to assess the genetic and environmental influences on extreme OM scores. As described earlier, DF analysis estimates the genetic and environmental contributions to the mean difference between an extreme group and the rest of the population.

Results of DF extremes analyses are summarised in Table 9.4. A 10% threshold (as indexed by the OM total scores) was used to define cases with the most extreme symptoms of OM at each age. At age 1.5 years, probandwise concordances were 85% for MZ twins and 66% for same-sex DZ twins. After transforming both proband and co-twin OM scores by dividing by the proband zygosity-specific mean (ensuring group means to be 1.0 for MZ and DZ probands), the co-twin means were .86 for MZ co-twins and .68 for DZ co-twins, suggesting moderate genetic influence. Application of DF group analysis to these data yielded a significant estimate of .33 for group differences heritability, indicating that about one third of the mean difference between the probands and the population can be attributed to genetic factors. The estimate of group shared environment was .60 indicating notable shared environmental influences on otitis media. The remaining 7% of the difference was due to nonshared environmental influence and error of measurement.

Probandwise concordances were 84% and 74% for MZ twins at ages 3 and 4 years, and for same-sex DZ twins 63% and 50% respectively. The transformed co-twin means at ages 3 and 4 years were .93 and .87 for MZ co-twins, and for DZ co-twins .64 and .63 at respective ages. DF group analyses of these data yielded similar group differences heritability estimates of .57 and .50 at ages 3 and 4 years

respectively, suggesting that over half of the mean difference between the probands and the population is accounted for by genetic factors. The estimates of group shared environment were .35 at age 3 years and .37 at age 4 years, suggesting notable shared environmental influences on otitis media in childhood.

Table 9.4 DF extremes analyses: Probandwise concordances, transformed co-twin means, group heritability, shared environment and non-shared environment estimates for same sex MZ and DZ twins for OM total score at ages 1.5 years, 3 years and 4 years.

	Probandwise concordance rate	Transformed co-twin mean (SE)	h_2g	c_2g	e_2g
Age 1.5 years					
MZ	85%	.93 (± .01)	.33	.60	.07
DZ	66%	.76 (± .03)			
Age 3 years					
MZ	84%	.93 (± .02)	.57	.35	.08
DZ	63%	.64 (± .04)			
Age 4 years					
MZ	74%	.87 (± .02)	.50	.37	.13
DZ	50%	.63 (± .04)			

Note: h_2g= group heritability estimate; c_2g=group shared environment estimate; e_2g=group non-shared environment estimate

9.7.2 Developmental Differences:

Children with persistent problems of OM (i.e. >90th percentile of the OM longitudinal aggregate total scale) were compared to the rest of the distribution for longitudinally assessed measures of language development (MCDI), non-verbal cognitive development (PARCA) and behaviour problems (RRPSPC). The table below (Table 9.5) summarises the findings of group mean differences. Analyses of variance indicated that children affected by OM scored significantly higher on behaviour problems at all ages of assessment ($p<.001$). At age 2 years children with extreme OM symptoms scored significantly lower on verbal ability ($p<.05$), but not at ages 3 and 4 years. For the observed mean differences effect sizes were

small. For non-verbal cognitive ability (PARCA) there were no significant differences between the groups at any age.

Table 9.5 Standardised mean scores behaviour problems (RRPSPC), language (MCDI) and non-verbal cognitive development (PARCA) and results of analysis of variance (ANOVA) between children affected and unaffected by otitis media at ages 2, 3 and 4 years.

		Otitis Media					
	Developmental Measure	***Unaffected****		***Affected****		***ANOVA***	
		Mean	***SD***	***Mean***	***SD***	***F***	***p***
2 years	**RRPSPC**	-0.05	0.99	0.31	1.04	41.92	.000
	MCDI	0.02	1.00	-0.16	0.96	11.35	.001
	PARCA	0.00	1.00	-0.01	0.98	0.08	.782
3 years	**RRPSPC**	-0.05	0.98	0.44	1.03	71.10	.000
	MCDI	0.01	1.00	-0.08	1.03	2.47	.116
	PARCA	0.01	0.99	-0.09	1.05	3.17	.075
4 years	**RRPSPC**	-0.06	0.97	0.46	1.11	81.71	.000
	MCDI	0.00	0.98	-0.04	1.17	0.52	.471
	PARCA	0.01	0.99	-0.08	1.08	2.41	.121

*Age 2 years N=2570
Age 3 years N=2630
Age 4 years N=2611

** Age 2 years N=380
Age 3 years N=320
Age 4 years N=339

9.7.3 Multivariate Analyses:

For the multivariate sample, phenotypic correlations were computed using the longitudinal aggregates between OM and developmental outcomes. Measures of language and non-verbal cognitive development showed virtually no association with otitis media at any age. The bivariate correlations were weak for non-verbal cognitive development (ranging from r=-.02 to r= -.04) and for language development (ranging from r=-.03 to r=-.06) between the ages 2 to 4 years. However, for behaviour problems moderate associations with OM were found at ages 2 (r=.19), 3 (r=.26) and 4 years (r=30).

Multivariate genetic analysis is based on cross-twin correlations for MZ and DZ twins which are shown in Table 9.6. The differences in cross-twin correlations on measures of OM and behaviour problems between zygosity groups suggest

modest genetic mediation of the correlations and substantial mediation due to shared environment.

Table 9.6 Cross-twin correlations (with 95% confidence intervals) for MZ and DZ groups between measures of otitis media (OM) , behaviour problems, language and non-verbal cognitive development at ages 2, 3 and 4 years

Zygosity, $N_{(pairs)}$	***Cross-twin Correlations (95% CI)***	***2 years***	***3 years***	***4 years***
MZ N=760	***OM-Behaviour Problems***	.21 (-.14 –.28)	.26 (.19 –.33)	.31 (.25–.38)
	OM-Language	-.04 (-.11 –.03)	.01 (-.06 –.08)	-.02 (-.09 –.05)
	OM-Non-verbal	-.01 (-.08 —.06)	.04 (-.03 –.11)	-.05 (-.12 –.02)
DZ N=715	***OM-Behaviour Problems***	.18 (.11 – .26)	.21 (.14 –.29)	.24 (.17 –.31)
	OM-Language	-.07 (-.14 – -.01)	-.04 (-.11 –.03)	-.06 (-.13 –.01)
	OM-Non-verbal	-.08 (-.15 – -.01)	-.06 (-.13 –.01)	-.04 (-.11 –.03)

As described earlier (see Chapter 3, Fig. 3.3), the correlated factors model (Neale et al., 1992) was used to examine the relationship between OM and behaviour problems more thoroughly. Maximum-likelihood model-fitting using variance/covariance matrices were applied at each age to the data using the statistical software package MX (Neale et al., 1999). The fit statistics are summarised in the table below (Table 9.7). The fit results indicate a good fit of the model to the data at all ages.

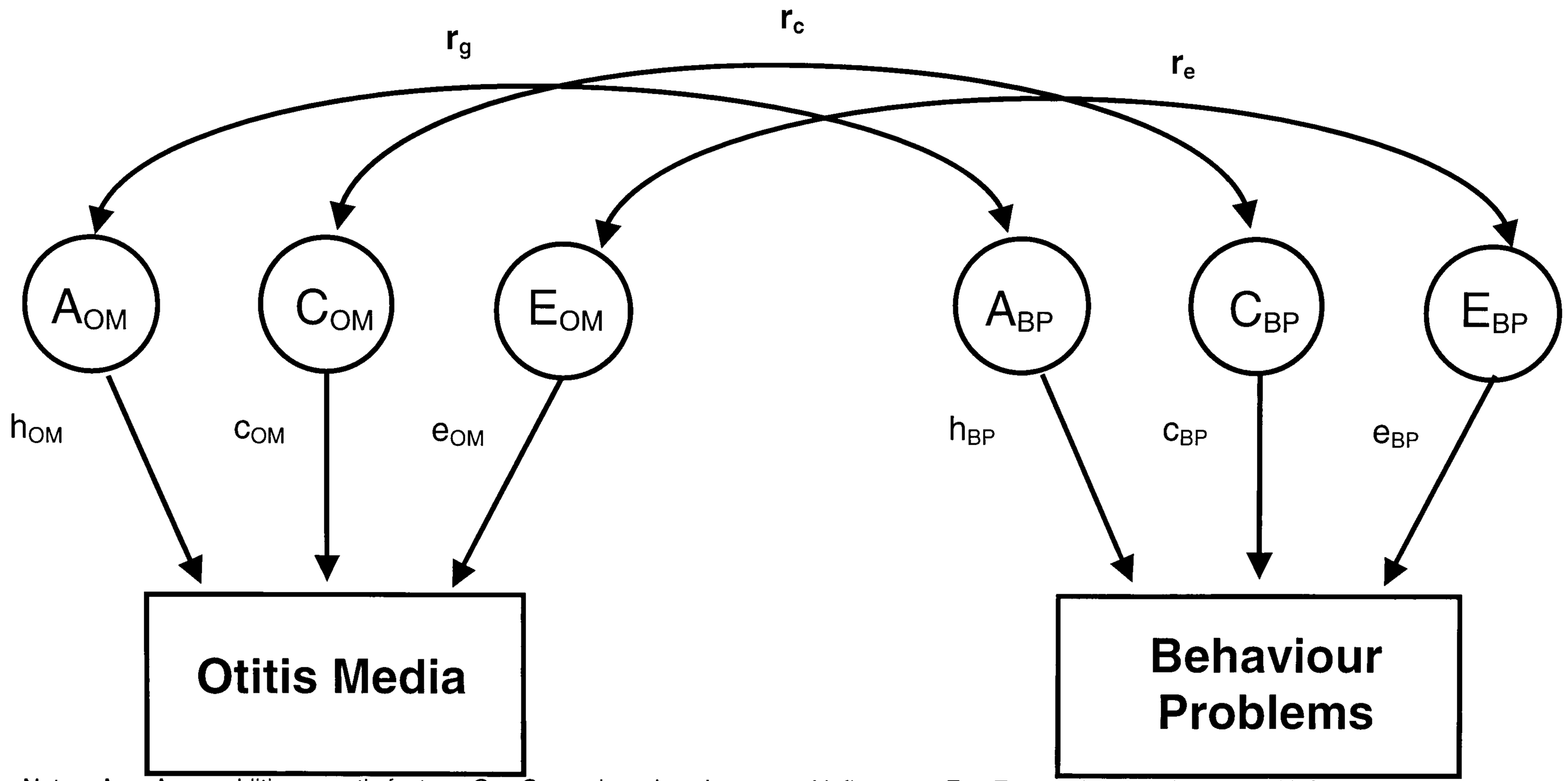
Table 9.7 Fit statistics and parameter estimates of bivariate genetic analyses of the association between otitis media (OM) and behaviour problem total score (BP) at ages 2, 3, and 4 years using the correlated factors model

	Model Fit Statistics				
	X^2	**df**	**p**	**AIC**	**RMSEA**
OM-BP 2 years	15.89	11	.15	-6.11	.019
OM-BP 3 years	8.11	11	.70	-13.89	.000
OM-BP 4 years	23.90	11	.01	1.90	.020

	h_{OM}	c_{OM}	e_{OM}	h_{BP}	c_{BP}	e_{BP}	r_g (95% CI)	r_c (95% CI)	r_e (95% CI)
OM-BP 2 years	.45	.82	.35	.52	.71	.47	.00 (-.13 - .13)	.33 (.25-.41)	-.01 (-.08 -.06)
OM-BP 3 years	.56	.72	.39	.50	.72	.49	.20 (.07-.33)	.40 (.31-.48)	.02 (-.05-.09)
OM-BP 4 years	.60	.71	.37	.58	.62	.52	.10 (-.01-.22)	.56 (.47-.66)	.10 (.03-.17)

The estimates of the bivariate genetic analyses are summarised in the above table (Table 9.7) and relate to the model shown in Figure 9.2. As described earlier, the correlated factors model breaks down the phenotypic correlation between two traits into its genetic and environmental components. At age 2 years the genetic correlation (r_G) between OM and behaviour problems was zero; at ages 3 and 4 years r_G was .20 and .10 respectively with little contribution of genetic factors towards the phenotypic correlation suggesting only slight genetic mediation (.01 and .03 at ages 3 and 4 years respectively). The bivariate heritability estimates were .04 (i.e., .01 / .26) at age 3 years and .10 (i.e. .03 /.30) at age 4, which indicates that genetic factors account for 4% and 10% of the phenotypic correlation between OM and behaviour problems at ages 3 and 4 years respectively. At both of these ages, most of the phenotypic correlation between OM and behaviour problems is due to shared environment rather than genetics: The shared environmental correlation at 2 years is .33 and increases to .56 at age 4 years. The contributions of shared environment to the phenotypic correlation ($c_{OM} \times r_c \times c_{BP}$) are .19, .21 and .25 at ages 2, 3 and 4 years respectively. The bivariate estimates of shared environment explain between 81% and 100% of the covariance.

Figure 9.2: Bivariate correlated factors model: Relationship between otitis media (OM) and behaviour problems (BP) assessed at ages 2, 3 and 4 years



Notes: A_{OM}, A_{BP} = additive genetic factors; C_{OM},C_{BP} = shared environmental influences; E_{OM},E_{BP} = unique environmental influences; h_{OM}, h_{BP}, c_{OM}, c_{BP}, e_{OM}, e_{BP} = parameter estimates of genetic and environmental influences; r_g = genetic correlation; r_c = shared environmental correlation; r_e = non-shared environmental correlation. Data values are provided in Table 9.7.

9.8 Conclusion

In this prospective twin study, the correlations for OM total score and individual symptoms were found to be consistently higher in MZ twins (.85 – .89) than in DZ twins (.46 – .67) indicating the presence of substantial genetic effects. Throughout early childhood, heritability of OM increased from 48% to 71% from age 1.5 to 4 years whereas the effects of shared environment decreased from 41-15%. These results are in line with findings from two previous twin studies (Casselbrant et al., 1999; Kvaerner et al., 1997) which also found a considerable genetic component to OM.

Kvaerner and colleagues (1997) reported higher heritability of OM in females (75%) than in males (45%). Although the present results suggest the presence of gender differences for individual symptoms of OM, the effect sizes were small and for the overall OM score no differences in parameter estimates between males and females were found.

In addition the findings show that symptoms related to airway blockage showed higher heritability than symptoms associated with acute infection. A possible explanation is that airway blockage as a result of ear infection may be directly related to the anatomy of the ear, whereas acute infection might be more closely related to the environment, particularly shared environment. Environmental effects are unlikely to be associated with cross infection of OM from one twin to another as in the present analysis, interactive effects between siblings were found to be negative and non-significant. This implies that for otitis media sibling interaction is unlikely to play a role in disease transmission between twin and co-twin.

These univariate results support strong genetic influence on chronic airway blockage and less but nonetheless substantial genetic influence on acute ear infection. The pattern of shared environmental influence is reversed. These

findings can be used in clinical work by asking questions about family history of chronic airway blockage as well as presentation in clinical practice, by paying more attention to children who have siblings or parents with otitis media or a known history of otitis media, especially with resultant airway blockage.

Multivariate analyses were used to explore the relationship between otitis media and child development from ages 2-4 years. Phenotypic correlations between OM and measures of language, cognitive development and behaviour problems yielded estimates of bivariate associations. Contrary to the expectation, the associations between OM and language development were small and non-significant across ages. However, findings indicated that OM is more strongly related to behaviour problems than to either language or cognitive development at all ages of assessment. Despite the substantial influence of genetic factors and the moderate effect of shared environment during early childhood for univariate estimates of OM and behaviour problems (Plomin et al., 2002), this first multivariate genetic analysis of the association between OM and behaviour problems indicated that OM is largely associated with behaviour problems for reasons of shared environment rather than heredity.

A limitation of the study is its use of parent assessments which was made necessary by the large sample size needed to provide reliable estimates of genetic and environmental parameters. As the OM scales are based on parent ratings it is not possible to ascertain the number of children which resulted in actual clinical cases with diagnosed recurrent or persistent otitis media. In addition for the developmental measures, in nearly all cases the same parent completes the child assessments for both twins. Thus, if parents who rate their children high on behaviour problems also rate them as high on OM, this might result in inflated estimates of shared environmental factors. However, the correlation between parent assessments and tester administered measurements *of* children's weight in TEDS is high (r=.77) suggesting that parent report data can be reasonably valid. In

addition, other studies comparing parent reported symptoms of OM with children's tympanometric and otoscopic records suggest that positively-reported symptoms of OM by parents provide reasonable validity (Daly, Lindgren, & Giebink, 1994; Engel, Anteunis, Volovics, Hendriks, & Manni, 1999; Engel, Anteunis, Volovics, Hendriks, & Marres, 2000). Furthermore, the heritability estimates for OM reported here are comparable to the results reported by Casselbrant et al (1999) where the status of OM was based on otoscopic assessments.

The link between OM and behaviour problems is largely mediated by shared environment. This finding suggests that the effects of OM on behaviour problems may be preventable in the sense that the effects of OM on behaviour problems are not a consequence of the genetic factors responsible for OM. However, more research needs to be done to identify the specific mechanisms by which shared environmental factors lead to the links between OM and behaviour problems. An obvious possibility is socioeconomic status. However, when socioeconomic status was partialled out from the correlations between OM and behaviour problems, the partial correlations were .20, .22 and .29 at ages 2, 3 and 4 years, and very similar to the respective zero-order correlations (.19, .26 and .30 respectively). Thus, socioeconomic status is not a major contributor to the association. Other shared environmental candidates include parental smoking and child care but these were not assessed in the present study. If as expected, the link between OM and behaviour problems were mediated genetically, it would be more difficult to break the link. These results should motivate the search for the specific shared environmental factors and ways to intervene to break the link between OM and behaviour problems.

In conclusion, the results of this study confirm a strong genetic component in otitis media, with similar heritability for boys and girls. Environmental factors shared by children growing up in the same family play a role in acute infection but not in chronic airway blockage. This knowledge can be used in clinical practice via

considering family history in decisions to test, refer and treat. OM is more strongly related to behaviour problems than to language or cognitive development. Despite the high heritability and only moderate estimate of shared environment of OM, the association with behaviour problems is due to reasons of nurture rather than nature. This finding suggests that behaviour problems are not an inevitable consequence of the substantial genetic effects on OM and may be preventable if the shared environmental factors responsible for the association can be identified.

9.9 Acknowledgements

An earlier version of the univariate analyses reported here has been published previously:

Rovers,M., Haggard,M., Gannon,M., Koeppen-Schomerus,G., & Plomin,R. (2002). Heritability of symptom domains in otitis media: a longitudinal study of 1,373 twin pairs. American Journal of Epidemiology, 155(10), 958-964.

10 General Discussion

10.1 Overview

This concluding section will start with a summary of the main findings followed by a discussion of the implications of the results in general, as well as in relation to molecular genetic research specifically. In addition, some limitations will be outlined and directions for future research will be considered.

10.2 Summary of Results

The genetic and environmental contributions to four common medical disorders as well as their relationship with developmental measures and differences between affected and unaffected individuals were investigated in early childhood within a large population sample of twins assessed at ages 2, 3 and 4 years.

10.2.1 Asthma

For asthma, the present findings indicate that asthma is predominantly influenced by genetic factors in children as young as 3 and 4 years. These results suggest that the genetic mechanisms involved in asthma operate from an early age, although longitudinal research is needed to prove that the genetic factors that affect asthma in childhood also affect asthma later in development

Substantial genetic influences on asthma were found (78-79%) whereas shared environmental influences were small and not statistically significant. There was some indication of mean gender differences with asthma consistently greater in boys than girls. Although there is no necessary connection between mean gender differences and heritability within gender, the analyses suggested somewhat higher heritability in girls than in boys at age 4 years. However, this

gender difference was not statistically significant. Asthmatic children had slightly but significantly higher mean scores for total behaviour problems as well as on the subscales for anxiety and hyperactivity than non-asthmatic children ($p<.001$). There were no significant differences between the groups for cognitive and language outcomes. Regarding bivariate associations between asthma and behaviour problems, the relationships were weak, which implies that it is unlikely that shared factors (environmental or genetic) exist that are common to the aetiology of childhood asthma and behaviour problems. In other words, genetic influences on asthma are largely independent of developmental outcomes.

10.2.2 Eczema

Similar to the results of asthma, the findings on eczema suggest high heritability and the absence of shared environmental effects. Univariate genetic analyses showed that genetic factors account for a large proportion of liability to eczema in childhood (76-87%) whereas common environmental factors do not seem to have an effect. In addition, there was some evidence for non-additive as well as additive genetic influence.

Also, similar to asthma, children with eczema scored significantly higher on the behaviour problems total score as well as on subscales for anxiety and conduct problems than children without eczema ($p <.05$). There were no significant differences between the groups for verbal and non-verbal cognitive development. Moreover, bivariate correlations between eczema and behaviour problems were insubstantial suggesting that it is likely that both phenotypes are influenced by independent factors.

10.2.3 Weight and Overweight

For weight and overweight genetic factors contributed substantially to both individual differences in weight throughout the distribution (48-54%) and to the

mean weight difference between overweight children and the rest of the population (35-60%). In contrast to other twin studies of adolescence and adulthood, the present findings also suggest that in childhood shared family environment is important.

The role of parental feeding behaviour was explored as a potential source of environmental influence on body weight. Twin correlations were high and very similar for MZ and DZ twins, suggesting substantial influence of shared environment on parent feeding style. Surprisingly, however, there was no relationship between parent feeding style and body weight, neither for twins nor for their parents. These findings imply that environmental factors other than parental feeding behaviours are important in influencing children's body weight.

Overweight does not seem to have important effects on cognitive/language outcomes or behaviour problems. Overweight and normal weight children scored similarly on assessments of cognitive and language development. There were also no significant differences for behaviour problems.

10.2.4 Otitis Media

For otitis media (OM), univariate analyses indicated substantial heritability which increased with age. In contrast, the influence of shared environment was moderate and declined with age.

In terms of developmental implications, children with extreme OM symptoms scored significantly higher on behaviour problems ($p<.001$) but they were not significantly different for verbal and non-verbal cognitive development. Furthermore, bivariate correlations indicated that there were no significant links between OM, verbal and non-verbal cognitive ability. However, OM showed a moderate yet significant correlation with behaviour problems ($r=.33$). Bivariate genetic analyses indicated that this association is mediated largely by shared environment rather than by genetic overlap.

10.3 General Implications

A common finding for all of the health related traits investigated in this dissertation is that heritability is substantial, even from an early age. Furthermore, the results imply genetic links between the normal and abnormal in the sense that they appear to represent the quantitative extreme of the same genetic factors that operate throughout the normal range of variation. For the two continuously assessed traits – body weight and otitis media – group heritability at the extreme end of the distribution was similar to the heritability found for the analyses of individual differences. These findings are in line with the QTL hypothesis which assumes that multiple genes affect common disorders and result in a quantitative continuum of vulnerability. In other words rather than being aetiologically distinct, these disorders may represent the quantitative extreme of the same genetic processes that operate throughout the distribution. Similarly, the same environmental influences that are involved in the normal variation throughout the distribution may be at work at the extreme. The notion that the same causal processes are likely to operate within the normal range as well as at the extremes would have important clinical implications for predicting and preventing these disorders.

Another important finding was that across traits the contribution of shared environment was generally only weak. Although shared environmental effects were moderate for body weight and otitis media symptoms when the children were younger, these effects decreased progressively with age implying that although these factors play a role during the early years they become less important with age. For asthma and eczema shared environmental influences were virtually absent and not significant. Overall, these findings imply that shared experiences in childhood do not seem to have a lasting effect on the development of these disorders.

Because shared environmental effects were largely absent, it is likely that the effect of non-shared environment (though small) may have a more important part to play in the aetiology of these disorders. For instance it is possible that some environmental influences – although being universally present – may have differential effects on individuals regarding their genetic tendency towards developing particular disorders, known as genotype-environment interaction.

The reported findings extend those of previous studies based on data from families, twins and adoptees that have found comparable estimates (see Chapter 2 for details).

A novel aspect of this dissertation was the attempt to explore shared aetiological links between disorders and development employing multivariate approaches. Generally, the evidence for the existence of such links was relatively weak. For weight, asthma and eczema, the phenotypic associations with cognitive/language outcomes and behaviour problems were insubstantial and cross-twin cross-trait correlations were insignificant suggesting that genetic and environmental factors that affect each disorder are independent from developmental outcomes. The exception was otitis media for which a significant association was found with behaviour problems. Contrary to the expectation of being mediated by shared genetic factors, this link was almost exclusively accounted for by shared environmental factors, suggesting the possibility that some shared environmental experiences are interrelated and may work in combination with each other in influencing the development of behaviour problems in children with otitis media.

In respect to developmental differences, there were only a few mean differences between children affected by the investigated disorders, mostly for behaviour problems. However, the effect sizes were small, indicating that there were no major behavioural consequences for any of the investigated disorders. On a more general note in respect to group differences, although they are often of

central public and social interest (e.g. comparisons of prevalence rates between or within populations), their significance has frequently been exaggerated. For instance, modest average differences between two groups for a particular trait or disorder are thought of as implying that most of the members within one group exceed the members within the other group. In addition, the magnitude of group differences as well as their predictive power tends to be small, although there still may be interest in their origins. Group differences, such as population prevalences, are important for studies of disease epidemiology, but they are of limited value when it comes to getting to the core of the aetiology of common disorders.

The fact that genetic influences on all of the disorders explored in this thesis are so substantial whereas shared environmental factors are unimportant may seem counterintuitive at first. This perceived inconsistency of behavioural genetic studies of *not* finding shared environmental influence for many medical disorders may be explained by the fact that exposure to the major environmental factors is now relatively widespread and possibly universal which would leave genetic factors as the perceived determinants towards individual disease risk (Tattersfield et al., 2002).

The significant increase in prevalence for many disorders over the last century cannot be explained by changes in gene frequencies per se. It is possible that particular environmental risk factors may have risen considerably more recently whereas these factors were less common during the beginning of the last century. Another possible explanation is that various pre-existing genetic factors are interacting with and responding to a dramatically changing environment (e.g. decline in infectious diseases, immunisations, changes in diet and others) and have rendered a large percentage of the population susceptible to various disorders.

Although all of the disorders are largely influenced by genetic factors, their underlying mechanisms are complex rather than simple. Intervention is most likely to be effective on an environmental level and the results imply that for all disorders non-shared environmental factors represent important targets for intervention. Hence, a better understanding of the specific environmental factors relating to lifestyles and behaviours that contribute to these disorders is critical in order to plan and implement effective prevention strategies.

Although genetic factors are likely to help to identify and target at-risk populations, behavioural and environmental factors are likely to represent the greatest opportunity for more immediate actions and interventions. Similar to additive genetic effects, it is also possible that in genetically predisposed individuals the combination of several environmental risk factors may have an additive or even a multiplier effect.

10.4 The Search for Genes

The fact that heritability is so considerable for all of the health related traits studied makes them attractive targets for molecular genetic research. Attempts are currently underway to identify genes for all of these disorders. Although environmental factors are mainly responsible for the general and rapid increase of the obesity epidemic, the regulation of body weight is substantially under the control of genetic factors. Over the last few decades there has been considerable progress in understanding the molecular genetic mechanisms related to obesity, particularly regarding appetite regulation and storage of adipose tissue. Although there are some instances where severe obesity is the result of a single gene effect, monogenic obesity tends to be the exception rather than the rule. Monogenic variants of obesity have helped scientists to understand the underlying mechanisms, but they are in themselves not very relevant to the common form of human obesity.

Attempts to find associations between DNA sequence variation in specific genes and obesity phenotypes continue to grow. To date numerous candidate genes have been found and several loci have been linked to obesity indicators in genomic scans and other linkage study designs. The most recent summary of the obesity gene map notes that the putative loci affecting obesity-related phenotypes can be found on all chromosomes and the number of genes, markers, and chromosomal regions that have been associated or linked with human obesity phenotypes currently exceeds 300 (Chagnon et al., 2003).

Similarly for asthma there has been great progress in the search for genes and several important discoveries have been made, especially over the last few years. Many genes appear to be related to different aspects of the main (allergic) mechanism that has been studied to date. Although asthma aetiology is partly based on this prominent allergic component, this fails to account for the fact that there are some individuals with hyperresponsive airways who are not atopic. Very recently, the ADAM33 gene has been reported to be associated with this disorder (Van Eerdewegh et al., 2002) and especially with the generation of bronchial hyperresponsiveness rather than the allergic and immunological components of asthma. Although this finding awaits further replication, a genetic link with hyperresponsive airways offers new avenues of research into the molecular genetic mechanisms underlying asthma.

In contrast to asthma and obesity, the genetic determinants of eczema have received somewhat less attention. Only recently, considerable efforts have started in the search for genes associated with eczema. Findings of several candidate genes as well as of linkage studies have been reported (e.g. Lee et al., 2000; Bradley et al., 2002; Haagerup et al., 2002) and it is likely that more important genes will be found in the future.

Although several important clues have started to emerge, the puzzle as a whole still awaits to be solved as several studies have found evidence for the

interrelationship between the three major atopic disorders (i.e. eczema, asthma and hay fever) (Strachan, Wong, & Spector, 2001; Lichtenstein et al., 1997; Diepgen & Blettner, 1996; Hopper et al., 1990). Despite this link it remains as yet unclear to what degree atopy is responsible for the expression of and any overlap between these disorders. Therefore, it is plausible to assume that, in addition to the "allergic disease genes," there are "phenotype-specific genes" or possibly certain combinations of susceptibility genes (e.g. gene-gene interactions) that contribute to the expression of asthma, eczema and hay fever (Barnes, 2000; Castro et al., 2001).

Also worth noting are two relatively recent reports which suggest that children with otitis media have higher rates for some atopy-related disorders (Caffarelli, Savini, Giordano, Gianlupi, & Cavagni, 1998; Alles et al., 2001). Both studies found that this difference was especially apparent for allergic rhinitis (hay fever). However, these results should be viewed with caution as they are based on relatively small clinical samples. In addition, although interesting, these findings do not imply that there is link between the aetiology of atopy and that of OM. However, it is possible that a common aetiological link may exist but this is at present speculative and awaits as yet future study.

In contrast to the other disorders investigated in this thesis, otitis media is generally a transitory and relatively benign condition of childhood. Hence, the search for OM related genes has probably been somewhat slower and less systematic than for other medical problems which tend to be more persistent and prominent public health concerns. Despite the evidence for a strong genetic component of OM, no susceptibility genes have been identified to date. Some of the symptoms that were included in the OM assessment scale used in TEDS (i.e. ear tugging, hearing problems during a cold, catarrhal discharge) are closely associated with upper respiratory infections. Hence, it is possible that particularly

for acute OM, the implicated genes are related to infectious processes of the middle ear as well as to those of the upper respiratory airways.

Not only would the identification of OM genes provide a deeper understanding of the pathophysiology of this common childhood disorder, but probably also of acute and chronic bacterial diseases in general.

For all of the health related traits investigated in this thesis, the genetic aetiologies are likely to be complex rather than simple. Even though several important susceptibility genes have now been identified for these disorders, the challenge remains to uncover how these genes interact with environmental risk factors, requiring progress in the field of molecular epidemiology (Rutter, 2002).

10.5 Limitations

The following section includes a brief outline of the extent to which the current findings can be generalised to other measures and populations. More detailed discussions of the limitations of individual analyses are covered in the earlier chapters.

10.5.1 Sample characteristics

Despite considerable attrition, the TEDS sample remains relatively representative of children in the UK, and is likely to reflect the characteristics of populations in the Westernised industrial nations.

The analyses reported in this dissertation were based upon twins who provided complete data for the relevant measures and sample comparisons for basic demographic variables throughout these studies suggest that sampling biases were minimal.

10.5.2 Measures and Analyses

The current findings are based on parent reports of children's illnesses, physical characteristics and behaviour in addition to parent-administered

assessments of twins' verbal and nonverbal cognitive development. It is therefore possible that in some instances over-reporting has occurred especially in relation to parent reported eczema and possibly also for otitis media (eczema can include other skin disorders and OM can include instances of upper respiratory infections). Hence, it is possible that different assessments, such as doctor diagnosed disease status or independently assessed measures of development would have yielded somewhat different results. However, it should be noted that the reported results are generally in agreement with findings previously reported in the literature. Moreover, if over-reporting or other types of parental reporting bias occurred, parents should report similar biases for both of their twins. This would be seen in these analyses as shared environmental influence. Finding little evidence for shared environmental influence suggests that such biases are not important.

10.5.3 Gene-environment correlations and interactions

The twin method assumes that genetic and environmental effects are uncorrelated and add up in a linear fashion and that gene-environment correlations and interactions are absent. Because it was not possible to explicitly test these assumptions within the present studies, it is possible that the heritability estimates derived from the current results include non-additive influences and the effects of genetic influences on exposure and sensitivity to environmental factors.

10.5.4 Assortative Mating:

The analyses in this thesis assumed random mating in the population. This assumption seems safe in that couples are unlikely to assort on traits related to their future offspring's health. In general, assortative mating is modest for personality, psychopathology and body weight, although assortative mating for cognitive abilities is substantial. Moreover, assortative mating has the effect of increasing estimates of shared environment in a twin study. Finding little evidence

for shared environment suggests that assortative mating is not a major factor for these traits.

10.6 Directions for future research

The combination of health psychology and behavioural genetics clearly has an important role to play, not only in conducting research to identify *where* and *when* linkages between particular behaviours and health outcomes occur, but also to study *how* they are mediated. An extended knowledge of the nature of the mechanisms through which particular behaviours contribute to health and disease is essential for devising preventative strategies and designing interventions which can make a significant contribution to public health in the future.

In addition to the importance of genetic factors, health and disease are also influenced by a multitude of environments (e.g. social, cultural, geographic and others). Although the dynamics between genes and environments in relation to health are starting to become better understood there is still a long way to go in this, and in other related aspects, such as disease prevention and control. A deeper understanding of the interplay between genes and the environment may, by identifying causal processes, point to appropriate sites for prevention or treatment. In this way, an extended understanding of the emergence of these disorders in early life may lead to better therapeutic targets so that useful interventions can be designed which can help to prevent the negative outcomes of the diseases. In addition, greater knowledge of aetiology also has the potential to improve the guidelines for classification and fine-tune and improve clinical diagnosis.

The present results represent a first step towards explaining the magnitude of genetic and environmental influences on health related phenotypes in childhood. However, the findings are only meaningful in relation to other behavioural genetic studies, and their importance should be seen as depending on replication in other

samples, using alternative research designs, and – most importantly – using other diagnostic assessments and developmental scales.

An attempt was made to explore the potential links between health related traits with development. Despite the fact that in most instances developmental outcome was weakly correlated with the respective health phenotype, bivariate relationships may strengthen as the sample gets older. Although further follow up studies as well as additional studies of other samples are needed to confirm the observations reported in this thesis, the present findings suggest that psychological implications in young children affected by a variety of medical problems are largely absent and are likely to be unrelated to the disorders themselves. Some of these investigations will continue as the TEDS twins are followed up into middle childhood and early adolescence.

Furthermore, data that are currently being collected will enable us to gain a more complete picture of links with and differences in behaviour problems between affected and unaffected children as it will be possible to compare parent and teacher ratings. In addition, these data will provide important answers in determining the potential effect of rater bias by parent assessments alone. Within the present analyses it was not possible to completely reject the presence of rater effects.

Even though all of the traits studied here show substantial genetic influence in childhood, the proportions of environmental effects are equally important. For future investigations it is therefore important to study both the genetic effects as well as the environmental factors in order to paint a complete picture of the diseases studied. Although TEDS itself was not designed to study the relationships between health related traits, associated environments and developmental links, it represents an important resource for future research projects. As the design of the TEDS study only includes a limited number of assessments in relation to the studied disorders, it was not possible to investigate links between genetic and

specific environmental risk factors systematically. However, spin-off projects like the E-risk study (which focuses on studying links with specific environmental risk factors (Caspi, Taylor, Moffitt, & Plomin, 2000; Moffitt, 2002) and the Eating Study (which explores associations between body weight, food and activity preferences) have the potential to uncover such links (Wardle et al., 2001; Wardle et al., 2002).

Another powerful approach for exploring nonshared environmental effects is to study MZ twins who are discordant for disorders. As MZ twins are genetically identical, any differences can only be due to environmental factors and approaches exploring the differences in disease status may be an important starting point for identifying specific environmental effects.

Research at the developmental interface between behavioural genetics and health psychology will continue to become increasingly important in the future. Findings from such studies will eventually help public health initiatives to identify environmental factors and target specific behaviours that are involved in the aetiology of many disorders.

It is necessary to know much more regarding the functions of specific genes and how they work. Research is beginning to identify genes that influence individual responses to drug treatments (pharmacogenetics) in addition to the way in which genes operate (functional genomics).

For future twin studies on health related phenotypes it will be important to include more sophisticated assessments of associations between genetic propensities and measures of the environment to find out how, where and under what specific circumstances nature and nurture work in concert.

11 References

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APPENDIX 1:

LITERATURE SEARCH 1980-2001
BEHAVIOURAL GENETICS and HEALTH PSYCHOLOGY

The following provides details of a literature search on the number of articles published between 1980 and 2001 in the disciplines of (1) behavioural genetics, (2) health psychology and related disciplines and (3) interdisciplinary overlap.

Using the OVID interface (www.ovid.com) the databases searched were the Medical Literature Analysis and Retrieval System Online (MEDLINE) and Psychological Abstracts (PsycINFO).

Explanatory notes on syntax and search history:

The search for "Behavioural genetics" relates to searches #1-108
The search for "Health psychology" includes searches #109-214
The search for interdisciplinary articles relates to searches # 215-236

List of Abbreviations used for OVID syntax

.sh	=	subject heading
.jn	=	journal
.ab	=	abstract
.ti	=	title
.kw	=	keyword
yr	=	year of publication
/xx	=	specifies a search restriction to an area; this is expressed by two letters followed by the name of the area in parentheses e.g. /ge [Genetics]

SEARCH HISTORY:

1. behavioral genetics.sh.
2. twin studies.sh.
3. nature nurture.sh.
4. behavior genetics.jn.
5. adoption study.ab,kw,ti.
6. adoption studies.ab,kw,ti.
7. twin study.ab,kw,ti.
8. twin studies.ab,kw,ti.
9. family study and (heritable or heritability).ab,kw,ti.
10. ((genetic or genetics) and family study and (environment or environmental)).ab,kw,ti.
11. ((genetic or genetics) and family studies and (environment or environmental)).ab,kw,ti.
12. shared environment.ab,kw,ti.
13. non-shared environment.ab,kw,ti.
14. (heritability and (environment or environmental)).ab,kw,ti.
15. sibling resemblance.ab,kw,ti.
16. multivariate genetic.ab,kw,ti.
17. univariate genetic.ab,kw,ti.
18. ((genetic or genetics) and cognitive ability).ab,kw,ti.
19. (nature and nurture).ab,kw,ti.
20. (genotype and environment and interaction).ab,kw,ti.
21. (heritable and (environment or environmental)).ab,kw,ti.
22. behavior genetics.ab,kw,ti.

23. behavioral genetics.ab,kw,ti.
24. behaviour genetics.ab,kw,ti.
25. behavioural genetics.ab,kw,ti.
26. (genetic and environmental contributions).ab,ti,kw.
27. (genetic and environmental influences).ab,ti,kw.
28. (genetic and environmental factors).ab,ti,kw.
29. *"Genetics, Behavioral"/
30. gene-environment interaction.ab,ti,kw.
31. (MZ and DZ).ab.
32. pregnancy.sh
33. 31 not 32
34. (co-twin and control).ab,ti,kw.
35. 34 not 32
36. (genetic and environmental contribution).ab,ti,kw.
37. (genetic and environmental influence).ab,ti,kw.
38. sibling correlations.ab,ti,kw.
39. (individual differences and (genetic or genetics)).ab,ti,kw.
40. behavioral genetic.ti,ab,kw.
41. behavioural genetic.ti,ab,kw.
42. *"Twins"/px [Psychology]
43. *"Twins"/ge [Genetics]
44. "Twins"/
45. "Genetics"/
46. 44 and 45
47. 46 not *"Twins"/hi [History]
48. 47 not *"Catholicism"/
49. 48 not *"Eugenics"/
50. 49 not *"Cloning, Organism"/
51. 50 not genetic determinism.kw.
52. 51 not "Genetics"/hi [History]
53. *"Twins, Dizygotic"/ge [Genetics]
54. *"Twins, Monozygotic"/ge [Genetics]
55. 53 and 54
56. Twin research.jn. and (genetic or genetics or gene or genes or heritable or heritability).ti,ab,kw.
57. *Asthma/ge [Genetics]
58. *Obesity/ge [Genetics]
59. *Cardiovascular Diseases/ge [Genetics]
60. *Alcoholism/ge [Genetics]
61. *Smoking/ge [Genetics]
62. (57 or 58 or 59 or 60 or 61) and (twin or twins or family or (genetic and environment) or (gene and environment) or (genetic and environmental) or (gene and environmental)).mp. [mp=ti, ab, rw, sh, hw, ty, id]
63. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 33 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 52 or 55 or 56 or 62
64. 63
65. limit 64 to yr=1980
66. limit 64 to yr=1981
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102. remove duplicates from 80
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106. remove duplicates from 84
107. remove duplicates from 85
108. remove duplicates from 86
109. health psychology.ab,ti,kw.
110. Health Psychology.jn.
111. Journal of Health Psychology.jn.
112. Psychology & Health.jn.
113. Behavioral Medicine.jn.
114. International Journal of Behavioral Medicine.jn.
115. *Health Behavior/
116. *Health attitudes/
117. *Eating/px [Psychology]
118. *Stress/px [Psychology]
119. *Obesity/pc, px [Psychology]
120. *Obesity/nu [Nursing]
121. 119 not 120
122. *Alcoholism/dh, px, ed [Psychology, Education]
123. Smoking Cessation/px [Psychology]
124. *cancer screening/
125. *Mass Screening/px [Psychology]
126. *"Eating Attitudes"/
127. biopsychosocial model.ti,ab,kw.
128. *"Disease Susceptibility"/px [Psychology]
129. "Psychoneuroimmunology"/
130. *"Low Back Pain"/px [Psychology]
131. AIDS.mp. [mp=ti, ab, rw, sh, hw, ty, id]
132. HIV.mp. [mp=ti, ab, rw, sh, hw, ty, id]
133. condom.mp. [mp=ti, ab, rw, sh, hw, ty, id]
134. (131 or 132) and 133
135. *"Condoms"/
136. "Coronary Disease"/px [Psychology]
137. ((breast or testicular) and self examination).ab,ti,kw.

138. (arthritis and (psychology or psychological)).ab,ti,kw.
139. (diabetes and (psychology or psychological)).ab,ti,kw.
140. (asthma and (psychology or psychological)).ab,ti,kw.
141. "Health Attitudes"/
142. exp Behavioral Medicine/
143. exp Asthma/pc, px [Prevention & Control, Psychology]
144. exp Obesity/dh, pc, px [Diet Therapy, Prevention & Control, Psychology]
145. exp Coronary Arteriosclerosis/pc, dh, px, ep [Prevention & Control, Diet Therapy, Psychology, Epidemiology]
146. exp Colonic Diseases, Functional/pc, px, ep [Prevention & Control, Psychology, Epidemiology]
147. exp Quality of Life/px [Psychology]
148. exp Psychosomatic Medicine/
149. *Diseases in Twins/di, pp, dt, pc, px, ep, th, et, ge, im [Diagnosis, Physiopathology, Drug Therapy, Prevention & Control, Psychology, Epidemiology, Therapy, Etiology, Genetics, Immunology]
150. *Obesity/et [Etiology]
151. "Case Report"/
152. (149 or 150) not 151
153. *"Liability, Legal"/
154. "Pregnancy"/
155. *"Chorion"/
156. 152 not (153 or 154 or 155)
157. 156 not Psychiatr$.mp,jn.
158. "Autistic Disorder"/
159. 157 not 158
160. "Mental Disorders"/
161. 159 not 160
162. "Mice"/
163. 161 not 162
164. "Rats"/
165. 163 not 164
166. "Anencephaly"/
167. 165 not 166
168. 167 not schizophreni$.mp. [mp=ti, ab, rw, sh, hw, ty, id]
169. 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 168
170. 169
171. limit 170 to yr=1980
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221. 93 and 199
222. 94 and 200
223. 95 and 201
224. 96 and 202
225. 97 and 203
226. 98 and 204
227. 99 and 205
228. 100 and 206
229. 101 and 207
230. 102 and 208
231. 103 and 209
232. 104 and 210
233. 105 and 211
234. 106 and 212
235. 107 and 213
236. 108 and 214

APPENDIX 2: Fit Indices in Structural Equation Modelling

χ^2 or chi-square is one of the most commonly used fit indices. It compares the observed covariance matrix with the expected covariance matrix. A χ^2 value close to zero indicates that there is no difference between the observed and the predicted matrices (i.e., there is a perfect fit). χ^2 is sensitive to changes in sample size. A useful feature of χ^2 is that the difference between two χ^2 s can be interpreted in the same way as χ^2 itself. This allows comparison of models with different degrees of freedom.

AIC ('Akaike's Information Criterion') A large negative number indicates a good fit. It is a so-called 'parsimony-based' index in that it will favour simpler models over more complex ones if the extra complexity does not improve the fit very much.

RMSEA ('Root Mean Square Error of Approximation') is an index which is useful in that it is relatively insensitive to changes in the sample size. The closer the index is to zero, the better the fit indicated. A value of 0.00 – 0.05 indicates a good fit, whereas scores between 0.05 – 0.08 are considered to be adequate. Values greater than .10 indicate a poor fit.

APPENDIX 3: Details of Questionnaire Items

1. ASSESSMENT OF TWINS' HEARING - MIDDLE EAR DISEASE SCALE (MEDS)

Parents were asked about their twins' hearing on three occasions. The background booklet at 18 months contained seven questions on otitis media whereas the 3-year and 4-year booklets included six items each. Answers were scored for each twin on a 4 point Likert scale (often – sometimes – occasionally – never).

Principal component analyses revealed a single principal component at each age. Since all items were highly interrelated (individual item loadings were all above .45) a total score was created for each age.

Details on individual items are as follows:

Background booklet:

Item	*Question*
1	During or after a cold, do either of the twins seem to have difficulty hearing?
2	During a cold, do either of the twins get a heavy yellow/green (catarrhal) discharge from their nose?
3	Do either of the twins pull, poke, or scratch their ears?
4	Do either of the twins' ears go red and look sore for a long time? (please note: an ear that has just been slept on may look red for a short time, and does not apply in this question)
5	Has pus or sticky mucus (not ear wax) ever leaked out of either of the twins' ears?
6	Do either of the twins breathe through their mouth, rather than through their nose?
7	Do either of the twins snore or make snorting noises during their sleep?

3-year and 4-year booklet:

Item	*Question*
1	During a cold, do either of the twins get a heavy yellow/green (catarrhal) discharge from their nose?
2	Have either of your twins ever had earache?
3	Has pus or sticky mucus (not ear wax) ever leaked out of either of the twins' ears?
4	Do either of the twins breathe through their mouth, rather than through their nose?
5	Do either of the twins snore or make snorting noises during their sleep?
6	Do either of the twins ever seem to ignore what people are saying?

2. PARENT ATTITUDES TOWARDS EATING (PATE) – included in the analyses of weight and overweight

Parents were asked about their twins' hearing on three occasions. The 3-year and 4-year booklets included the following list of 7 items. The answers to items 1-6 were scored for each twin on a 5 point Likert scale in the direction of 1=disagree, 2=slightly disagree, 3=do not agree or disagree, 4= slightly agree and 5=agree. Item 7 was reverse scored (i.e. 1= agree to 5= disagree).

3-year and 4-year booklet:

Item	*Your Child's Diet*
1	When my child does not finish dinner, s/he should not get desert.
2	My child should always eat all of the food on his/her plate.
3	Generally, my child should only be allowed to eat at set mealtimes.
4	My child often has to be strongly encouraged to eat things s/he doesn't like because those foods are good for him/her.
5	My child should be told off for playing or fiddling with food.
6	I have to be especially careful to make sure my child eats enough.
7	Generally, it is OK for my child to snack and I don't worry about it.